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BUREAU OF HYGIENE AND TROPICAL DISEASES.

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ANTI-RABIES TREATMENT.

A Discussion of its Value in the Light of Recent Experimental Work.

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Introduction.

Anti-rabies treatment was introduced into human medicine by Louis Pasteur and his associates in Paris in 1885. Pasteur had found that the common rabies virus of the natural disease in dogs, or street virus, when passaged intracranially in rabbits, ultimately became fixed in its properties—*virus fixe*, or fixed virus. He further showed that fixed virus could be attenuated in virulence by drying an infected rabbit cord in a desiccating jar. The longer the cord was left to dry the less became the infectivity. Using cords of gradually increasing virulence, Pasteur was able to treat dogs so that they withstood a subsequent test inoculation of virulent virus (Pasteur, Chamberland and Roux, 1884). Encouraged by the results in dogs, Pasteur decided to try the treatment in human beings. The first case treated was a success, as the patient, badly bitten, developed no signs of rabies (Pasteur, 1885). The treatment was at once made available in Paris, and by 1886 nearly 2,500 people had been treated there (Pasteur, 1886). Pasteur's method was quickly adopted in all parts of the world, either in its original form, or after substantial modification. The most important modification was the use of chemical, chiefly phenolized, vaccines containing inactivated virus.

For the past 50 years or more the orthodox treatment of persons bitten by suspectedly rabid animals has been a course of anti-rabies vaccine. It is accordingly very difficult to obtain "control" figures that can be used in assessing the value of anti-rabies treatment.

Of recent years a considerable amount of experimental work has been performed on active immunization, and it has been learnt that it is difficult to prevent rabies in experimentally infected animals if the vaccine is given after infection. It has also been shown by Webster and other American workers that a number of phenolized vaccines available for veterinary and human use have been devoid of immunizing activity (see below). For these and other reasons there has been a growing feeling that anti-rabies treatment of man, as at present practised may not be as effective as it was originally believed to be. It may be said in general that French workers are convinced of the value of treatment, either with attenuated or chemical vaccines. Many British and

American workers, on the other hand, are somewhat sceptical. A critical review on the value of anti-rabies treatment published by WEBSTER (1939 *a*) has brought the subject very much into prominence.

It is my object to discuss the scientific basis on which anti-rabies treatment rests, with particular reference to recent experimental work. At the same time I shall try to explain some of the variable factors that make the evaluation of this treatment in human beings so difficult. Fuller references to many of the points raised will be found in an earlier publication (VAN ROOYEN and RHODES, 1940).

Some Features of Rabic Infection in Man.

Some properties of the rabies virus.—Rabies, as it occurs in nature, is caused by an agent known as *virus de rage de rue* or street virus. This agent is commonly accepted as being a filterable virus, although it is regarded by some as a protozoon, on account of the resemblance of the characteristic Negri inclusion body to certain protozoa. Street virus can be transmitted to laboratory animals such as monkeys, rabbits, guineapigs and mice, by peripheral or intracranial injection. After peripheral injection, *e.g.* in the muscles, virus remains viable locally for at least 4 days, invades nerve fibres within 24–48 hours, and spreads to the cord along these channels (HABEL, 1941 *b*). There is no evidence that the blood stream is concerned in the dissemination of the virus to any significant extent after peripheral injection. Virus has been recovered, and histological changes have been found, most readily in the portion of central nervous system corresponding to the site inoculated (GOODPASTURE, 1925; WEBSTER, 1937, 1939 *b*; KLIGLER and BERNKOPF, 1943). Rabies infection can also be induced by direct intraneural injection of virus. Not only does street virus spread to the central nervous system centripetally after peripheral injection, but it also spreads out centrifugally therefrom along other nerves. By the end of the incubation period virus is probably widely disseminated throughout the peripheral and central nervous systems. The term *septinévrite* is applied to this essential neurotropic property.

After intracranial inoculation of street virus in, for example, rabbits or guineapigs, symptoms of rabic infection develop in about 14–20 days. If the brain of such an animal is passed intracranially in series it will be found that the incubation period becomes progressively shorter, and eventually "fixed" at about 5–8 days. The virus is now known as *virus fixe* or fixed virus, and is remarkably stable in its properties. Negri inclusion bodies are not normally formed by fixed virus.

It is probable that strains of street virus may vary considerably in virulence for man. Thus certain strains, found particularly in wolves and known as *renforcé* strains, produce paralysis in rabbits on intracranial inoculation after a shorter incubation period than usual. Such strains may become fixed after only a few intracranial passages. At the other end of the scale is the *oulou fato* virus of indigenous African mad-dog disease. These strains are of definitely reduced virulence for man. Although it has been suggested that *renforcé* strains are associated with unusually virulent infections, failing to respond to anti-rabies treatment, the position does not seem to be sufficiently clear for a definite statement to be made on this point (PROCA and BOBES, 1940).

Fixed virus does not infect the experimental animal so readily as street virus by peripheral routes, and does not show *septinévrite* to the same degree. Fixed virus is probably of considerably reduced virulence for man and may even be non-pathogenic on subcutaneous inoculation, unless large quantities are injected.

Observations that have been made on the antigenic structure of rabies viruses do not point to any marked differences between strains (see HAVENS and

MAYFIELD, 1933). It would be in keeping, however, with the newer knowledge of viruses if future work showed strains to differ considerably one from another. In recent years such antigenic variations have been found in strains of poliomyelitis and influenza viruses, for example.

Sources and modes of human infection with rabies.—Rabies exists in nature as an enzootic in dogs, wolves, jackals, mongooses and other animals, and may be transmitted to man, as it were accidentally, by the bite of a rabid animal. The majority of bites treated in anti-rabies institutes throughout the world are inflicted by dogs. In India about a third of all bites are inflicted by jackals, and in parts of Europe wolf bites are relatively frequent.

Dogs, especially in tropical climates, are liable to bite human beings apart altogether from rabies ; by no means all dog bites, therefore, even in countries where rabies is endemic, are inflicted by rabid animals. It is thought that only about 50 per cent. of rabid dogs actually excrete rabies virus in their saliva (WEBSTER, 1942) ; presumably, therefore, only one in every two rabid dogs is actually a source of danger to persons it may bite. Wolves and jackals are said seldom to bite man unless rabid.

On occasions rabies may follow scratches or licks of rabid animals, but this must be regarded as a great rarity. It is likewise most unusual to contract rabies from animals other than the four already mentioned. [This survey does not include rabies in Trinidad where the virus has been shown to be transmitted by species of vampire bat.]

Pathogenesis of human rabies.—After the bite of a rabid animal, virus probably remains localized in the wound for 24–48 hours, and then invades nerve fibres. Virus may persist locally, as it has been isolated from the scar (PACE, 1903). Virus has been recovered from nerve fibres in man on various occasions (PASTEUR *et al.*, 1884 ; BARDACH, 1888 ; ROUX, 1888, 1889 ; PACE, 1903), and histological changes have been found in the nerves of the bitten limb and corresponding spinal ganglia (MARINESCO and DRAGANESCO, 1932). *Septinévrite* occurs in man as in animals, and virus has been isolated from nerves other than those of the bitten limb ; histological changes may also occur (MANOUÉLIAN, 1936).

All the evidence points to the virus being disseminated in the body by nerve tracts, and not to any significant extent by blood or lymph. It is held by many that the length of the incubation period is related to the distance of the wound from the spinal cord or medulla, *i.e.* to the length of the nerve paths to be travelled by the street virus. For instance WEBSTER (1944) gives the following average incubation periods :—

bites on head, face and neck—30 days ;
bites on upper extremity—40 days ;
bites on lower extremity—60 days.

JOHNSON (1943), however, maintains that more important factors are the amount of virus inoculated into the wound, and the type of tissue bitten. The shortness of the incubation period after wounds on the head, face and neck is ascribed to the frequently severe nature of these bites, and the abundance of nerve filaments available to be invaded.

It is not known how long street virus takes to reach the central nervous system from a peripherally situated bite. It is presumably present in the central nervous system for several days before the onset of symptoms, and during this time centrifugal spread along nerves is taking place.

In certain circumstances it would appear that rabies virus can remain latent in the body, without causing symptoms, especially if anti-rabies treatment has been applied ; for rabies has developed after an incubation period of as long as 3 years (IYENGAR, 1935). In some cases that develop unusually late the onset of the disease may be provoked by an emotional shock (REMLINGER, 1946).

The minimal amount of virus required to infect man is not known, nor is it known if sub-infective doses inoculated in a wound in untreated persons can invade nerve paths, and set up an asymptomatic infection. There is some evidence that man has an innate resistance to rabies, at any rate to the common type of canine street virus, perhaps because the disease is normally spread from dog to dog, and the agent is not well adapted to invasion of human tissues.

Mortality from rabies in untreated persons.—Once rabic symptoms develop, the disease is invariably fatal, but only a comparatively small percentage of persons bitten by rabid animals actually develop rabies. It is extremely difficult to estimate scientifically the chances of dying of rabies following the bite of a rabid animal. Mortality figures should be based on observations made in the groups of persons bitten by known rabid animals, none of the bitten being treated in any way. All the persons in question would have to be observed for a year or more to make certain that rabies did not develop. Statistics of this type are not available. Numerous observations on groups of bitten persons untreated but selected to a greater or lesser extent, suggest, however, that an average mortality figure is from 5 to 15 per cent., this being modified by a number of factors. Thus, the mortality is higher in wolf bites, probably over 60 per cent., especially if situated on the face. The mortality is higher in deep than in superficial wounds, in wounds on the face, in multiple wounds and in wounds inflicted through bare skin (see HARVEY and MCKENDRICK, 1923). In fact the mortality from rabies in untreated persons is directly proportional to the amount of virus deposited in the wound by the biting animal, and to the degree of trauma inflicted on the tissues.

Cauterization of bites of rabid animals.—The orthodox " first-aid " treatment of bites inflicted by rabid animals is cauterization, by the thermocautery or by strong agents such as corrosive acids. Experimental work on guineapigs infected by intramuscular injection has shown that application of iodine, or washing with soft soap and water, is as effective, and does not cause scarring (SHAUGHNESSY and ZICHIS, 1943). Experimental observations suggest that cauterization may itself protect against rabies, even if applied up to 24 hours later (CABOT, 1889 ; POOR, 1911 ; ROSENAU, 1935). Even if promptly applied, however, it may fail to protect some animals (BABES and TALASESCU, 1894). Presumably in such cases the cauterizing agent fails to reach virus lying in " pockets ".

HARVEY and MCKENDRICK (1923) reported that efficient cauterization reduced the chances of developing the disease in the proportion of 4 : 3. MACKIE (1928) found it advantageous to open up wounds and wash with acriflavine. I have tried, but without success, to obtain more recent figures from Pasteur Institutes relating to the value of cauterization. From what has been said it will be evident, nevertheless, that cauterization has a definite protective effect. This is one of the many factors that complicate the evaluation of anti-rabies treatment, as both treatments are frequently given together.

Experimental Observations on Active Immunity in Rabies.

Animals can be immunized by anti-rabies vaccines given prior to infection. Under certain circumstances they can be protected from rabies by injections of vaccine given after infection.

Type of vaccine.—Numerous preparations have been used to induce active immunity in animals ; the more important are as follows :—

(*a*) Living or attenuated *virus fixe*, prepared as in Pasteur's or Hoegyes's method, can be used, and is an effective immunizing agent, but is not widely employed owing to the risk of death if large quantities are given. It was found that fresh living *virus fixe*, used as an adjunct to the phenolized virus, immunized

dogs more effectively than any other method (SHORTT *et al.*, 1934–5). WEBSTER (1939 *b*) using mice also found live virus vaccines to be effective immunizing agents.

(*b*) Chemical vaccines of various types have been much used. Phenol, chloroform, ether and formol inactivate rabies virus if left in contact for a sufficient time, and if used in adequate concentration. The process of inactivation is gradual, and chemical vaccines are sometimes used at a stage when virulent virus can still be detected by animal inoculation. More usually, however, chemical vaccines are used when the virus appears to be destroyed, and no sign of infection can be detected in inoculated animals. We know so little about the true biological nature of living rabies virus that it is perhaps unwise to assert that these vaccines contain "dead" virus. All that can be said is that with products such as Semple's phenolized vaccine, tests for infectivity consistently prove negative. Whether a "killed" chemical vaccine contains virus in a form that may be reactivated *in vivo* is not known. It is perhaps more appropriate to refer to chemical vaccines as containing "inactivated" virus.

Provided that the vaccine contains a sufficient quantity of virus material, and that the strain is of high immunizing potency (see below), a satisfactory state of resistance can be induced in laboratory animals, to a peripheral test dose, and even to an intracranial injection. Injections must be given repeatedly, and in large doses; for example, a monkey may require as much vaccine as is used for a human being. WEBSTER (1939 *b*), using a phenolized and a chloroformized vaccine, found that mice required a dose approximately five times as great as that advocated per gramme of body weight for man. There is some evidence that chloroformized vaccines are better immunizing agents than phenolized products. Etherized and formolized vaccines are also used.

(*c*) Virus grown in tissue culture can be used in its live state, formolized, or attenuated by ultra-violet light (HODES *et al.*, 1937, 1940; WEBSTER, 1937, 1938; KLIGLER and BERNKOPF, 1938, 1941; WEBSTER and CASALS, 1941).

(*d*) The principle of attenuation by exposure to ultra-violet light has also been extended to infected brain tissue (SANKARAN and BEER, 1934–5; WEBSTER and CASALS, 1940 *a*, 1941, 1942 *a*, *b*; LEVINSON *et al.*, 1944). It is almost certain that the virus is not completely destroyed in these vaccines, as they become less effective if inactivated for too long. Such vaccines are the most potent yet produced, and mice have been protected with them against 10,000 lethal (LD_{50}) doses of virus, whereas a chloroformized vaccine protected against only 1,000 lethal doses (WEBSTER and CASALS, 1942 *a*).

(*e*) Virus inactivated by the photodynamic action of methylene blue is antigenic, but probably only if some live virus remains in the preparation (GALLOWAY, 1934; SHORTT and BROOKS, 1933–4, 1934–5).

The strains of virus fixe used in vaccine production.—Anti-rabies vaccines are usually prepared from the classical Pasteur strain of *virus fixe*, of which a number of "off-shoots" are maintained in various institutes. It was found that the Pasteur strain was a more efficient antigen than *virus fixe* prepared from strains isolated in India (CUNNINGHAM *et al.*, 1933; SHORTT *et al.*, 1934, 1937).

The most important recent work in this connexion is that of HABEL (1940 *b*) who examined 31 strains of *virus fixe*, of which 25 were derived from the original Pasteur strain. He made the important observation that these strains differed considerably in their ability to immunize mice. He suggested that a high immunizing potency against a heterologous test virus is not an inherent characteristic of a strain, but can be altered during transfer. HAMPIL and ROBERTS (1942) made similar observations, and showed that substrains of the

same strain varied considerably, and might afford only slight protection even against the homologous virus.

With any given strain of *virus fixe*, the greater the amount of virus material the greater is the immunizing capacity of the vaccine. It is therefore desirable to ensure the maximum content of virus in the brain tissue used in the vaccine, and for this purpose HABEL (1941 *a*) recommends that animals be inoculated with dilute rather than concentrated suspensions of passage brain.

Laboratories preparing anti-rabies vaccines should periodically test the properties of their strain of virus along the following lines (HABEL, 1940 *b*): specificity should be checked by a neutralization test with antiserum; samples should be removed during the process of treatment with chemicals and tested for virulence in mice; attenuated vaccines should be similarly tested; mice should be immunized with the vaccine as ready for issue, and tested by intracerebral injection.

Technical methods in testing active immunity.—In tests for the immunizing potency of vaccines it is customary to inject the subsequent test or "challenge" dose of live virus by a rate that kills as nearly as possible all the control unvaccinated animals. Unless this dose is given intracerebrally or intraocularly, it is often difficult to secure infection of more than 50–75 per cent. of controls.

Various workers, using relatively ineffective vaccines, have experienced difficulty in immunizing animals sufficiently to withstand intracerebral or intraocular injections of test virus, although a peripheral injection might be resisted (see WEBSTER, 1939 *a*, 1942). Live vaccines and the newer irradiated and chloroformized vaccines will definitely protect against a subsequent intracranial test dose.

In all tests of this type an accurately titrated amount of virus must be used for estimating both the immunizing dose and the "challenge" dose; for this purpose it is usual to inject mice intracerebrally with falling serial tenfold dilutions, using at least 6 mice per dilution. The LD_{50} or 50 per cent. mortality endpoint, which is a convenient measure of the potency of the inoculum, is then calculated. The method introduced by REED and MUENCH (1938) gives additional accuracy to this calculation.

Vaccines are now usually assayed by a mouse test such as that introduced by WEBSTER (1939 *b*, 1940, 1941), which is carried out as follows: The vaccine to be assayed is diluted 1/10, and 1/8th of the stated dose is used (representing 1/80th). A total of 32 three-week-old mice are needed. In the case of canine vaccines one dose is given intraperitoneally to each of 16 of the mice. In the case of vaccines intended for human use, the mice are given 3 to 6 injections. Three weeks after the first injection of vaccine, the test and the 16 control mice are each divided into four lots and injected intracerebrally with 1, 10, 100 and 1,000 lethal (LD_{50}) doses. To detect a weak or immunizing effect the challenge dose can be given intramuscularly, from 2 to 32 lethal doses being used. Both test and control mice are examined for 60 days.

Somewhat similar tests have been introduced by WYCKOFF (1940–1; WYCKOFF and BECK, 1940; WYCKOFF and TESAR, 1941) and HABEL (1940 *a*). HABEL considered that the minimum requirement of a vaccine tested by his method was that it should protect against at least 1,000 lethal doses calculated by the 50 per cent. end-point method.

WEBSTER regarded the mouse immunity test as of considerable value in indicating the immunizing efficiency of anti-rabies vaccines, and it certainly appears to be by far the most practical, and at the same time accurate, method available. REMLINGER and BAILLY (1943), however, question whether mice are really suitable for such tests, and suggest that they are unduly susceptible to rabic infection.

Dogs have also been used extensively in testing anti-rabies vaccines, and, in general, a vaccine proved potent by mouse test proves effective when tested in dogs (JOHNSON and LEACH, 1940, 1942; LEACH and JOHNSON, 1940, 1942; WEBSTER and CASALS, 1940 *b*).

It may be argued that some of these tests are too severe, and in many ways the most valuable method of testing the immunizing potency of vaccines is to attempt to imitate what happens when they are used in human treatment. Thus, monkeys may be "challenged" by street virus injected intramuscularly, or, better still, saliva from rabid dogs could be employed.

WEBSTER (1939 *b*, 1940) tested a large number of commercially prepared vaccines available for sale in the U.S.A. for use in human anti-rabies treatment, and for the prophylactic immunization of dogs. With the exception of one product he found that the phenolized vaccines failed to immunize mice against a subsequent intracerebral challenge dose of even one lethal dose; chloroformized preparations were somewhat more effective. With dogs, chloroformized vaccines were found to give protection if the challenge dose was given intramuscularly, the phenolized vaccines studied in this work being valueless (see also WEBSTER and CASALS, 1940 *b*, 1942 *a*; LEACH and JOHNSON, 1940).

A considerable amount of work has been carried out on the mass prophylactic vaccination of dogs as a means of controlling rabies, and it has been customary to give only one injection. The observations of Webster just quoted showed, however, that the bulk of canine vaccines sold for the purpose were quite unable to confer a significant degree of immunity after a single injection. If large or repeated doses of potent phenolized or chloroformized vaccines are used, a high degree of immunity can be acquired, and the irradiated type of vaccine is even more potent.

Anti-rabies treatment of experimentally infected animals.—As has been seen above, it is perfectly possible to immunize animals by injections of potent vaccines containing live or inactivated virus given prior to the test dose of living virus. Immunity of this type has little direct bearing on anti-rabies treatment of man, however, where the course of vaccine has to be administered after the infection has been initiated. Accordingly, a number of workers have tried to prevent rabies from developing in animals infected by peripheral routes, by giving courses of anti-rabies vaccine after infection, and, in general, have found it difficult to achieve protection (for references see WEBSTER, 1939 *a*, 1942).

For example, extensive work, chiefly with monkeys, was carried out over a period of years in India, using chemical vaccines. Although some degree of protection was shown, the results were disappointing, as it was not possible to protect as many as 50 per cent. of animals, if the treatment was given after infection was initiated (CUNNINGHAM and MALONE, 1930; CUNNINGHAM *et al.*, 1933; SHORTT *et al.*, 1934, 1934–5; COVELL *et al.*, 1936–7).

Certain workers have been more successful. FERMI (1908), for instance, treated rats with large doses of vaccine after infection, and secured a significant degree of protection. More recently, HABEL (1940 *a*), working with guineapigs infected intramuscularly, was able to protect 16/27 by a series of 21 daily injections of 0·5 cc. phenolized vaccine; 4/5 controls developed rabies. It may be noted that the dose of vaccine used was very large, as compared with the dose recommended for human treatment. In another series of experiments, mice infected intramuscularly with street virus were not protected by subsequent injections of phenolized virus, although chloroformized vaccines occasionally protected; when five doses of an irradiated vaccine were given rabies was prevented in most instances (WEBSTER, 1939 *b*; WEBSTER and CASALS, 1942 *a*).

It may be concluded, therefore, that it is difficult to protect laboratory animals by anti-rabies treatment given after infection. Large doses of chloroformized, phenolized and particularly the potent irradiated vaccine, may, however, secure protection in the smaller laboratory animals. A powerfully protective effect of vaccines in infected monkeys has yet to be shown.

Serum therapy in experimental rabies.—Virus-neutralizing antibodies develop in the blood of infected animals and human beings. Powerfully rabidicidal sera can be produced by hyperimmunization of animals, for instance in sheep or rabbits by inoculation of phenolized virus followed by the living agent (SHORTT *et al.*, 1934–5 ; HABEL, 1940 *b*, 1945).

A number of workers have shown that rabies can be prevented in experimental animals by injections of antiserum given just before or just after injection of the virus. For example, antiserum can protect mice when injected before an intracerebral test dose, and is effective even up to 4 days later (HOYT *et al.*, 1936 ; HOYT and GURLEY, 1937–8, 1938). Other recent workers have also demonstrated the protective effect of serum (*e.g.*, PROCA *et al.*, 1935 ; YEN, 1942 ; FRIEDEMANN *et al.*, 1944). Special mention must be made of the observations of HABEL (1945) who worked with guineapigs and mice. He found that serum was most effective when given intramuscularly at the site of inoculation, and immediately after the virus. The treatment of infected animals with serum gave consistently better results than vaccination alone. The best results were achieved when serum was followed by vaccine treatment 6 days after the administration of the serum.

Mode of operation of anti-rabies treatment in experimental infections.—We have seen that courses of potent anti-rabies vaccine given before, and in certain circumstances after, infection can protect the experimental animal from rabic infection. What immunity mechanisms are involved ? Is there a different explanation for immunity produced by live virus, by " killed " virus, and irradiated virus which is probably attenuated and not actually destroyed ?

When the vaccines are given before infection there is ample time for the body to build up protective mechanisms in the ordinary way, and in the active immunity acquired by this method there are probably two main mechanisms concerned. Serum virus-neutralizing antibodies presumably play some rôle, although they cannot always be detected in animals which are nevertheless resistant to infection. The beneficial effects of rabies antiserum on experimental infection, presumably due to destruction of virus at the site of inoculation, should be recalled. Secondly, the immune tissues appear to exert some direct virus-neutralizing effect (KUBES and GALLIA, 1944). It has been shown that when virus is introduced into the tissues of an actively immunized animal it disappears from the site of inoculation more quickly than in a normal animal, and probably does not invade nerve tissue at all (HABEL, 1941 *b* ; KLIGLER and BERNKOPF, 1943). The reticulo-endothelial system may also be concerned, as the immune state is said to be abolished by " blockade " with Indian ink (LOEFFLER and SCHWEINBURG, 1933–4).

It is difficult to see how this more or less direct neutralization of virus by serum or tissue can play a part in the immunity acquired by post-infection treatment. The course of injections cannot stimulate the production of significant amounts of antibody for several days, and by this time the invading street virus must have progressed far along nerve tracts *en route* to the central nervous system, and be no longer accessible to circulating antibodies. Two alternative suggestions can be advanced to account for the resistance undoubtedly acquired under certain circumstances by animals subjected to anti-rabies treatment after infection :—

(1) It may be assumed that the infecting virus does in fact invade and pass along nerve tracts. This process takes time, and before the virus has reached

the central nervous system, the course of injections of vaccine has rendered the normally susceptible nerve cells resistant to invasion. Serum antibody may play some part, though probably small, in this neutralization. It may neutralize any virus remaining in the wound, but cannot affect that in nerve tracts. The antigen in the vaccine injected subcutaneously must be absorbed by the lymph or blood, so that it can reach the nervous system ahead of the street virus. If the vaccine contains live virus, presumably some particles of *virus fixe* may invade nerve fibres and spread to the central nervous system by this route. As large quantities of vaccine are always given, it is certain that the bulk of the virus must be absorbed from the site of injection by the lymph or blood stream.

The immunity, according to this suggestion, must be chiefly dependent upon an acquired resistance of the nerve cells.

(2) Of recent years much has been learned about a phenomenon of virus immunity known as " interference ". Thus, it has been shown that under certain conditions the presence of one virus may interfere with and prevent the growth of a second, usually closely related, virus. For example, mixtures of Rift Valley fever and yellow fever viruses, when inoculated in the monkey, did not prove so pathogenic as yellow fever virus alone (FINDLAY and MACCALLUM, 1937).

HENLE and HENLE have carried out important studies using influenza virus exposed to ultraviolet irradiation as an interfering agent (1944 *a*, *b*, 1945 *a*, *b*). Thus, in experiments in eggs, they showed that virus almost completely inactivated by ultra-violet light was capable of preventing the multiplication of active virus introduced into the same egg some hours later, or a short time earlier. Although virus might be prevented from multiplication by the interfering dose it was not actually destroyed. The interfering agents in these experiments were found to be the elementary bodies themselves.

For interference to occur in virus infections the interfering agent must, apparently, be living, or else attenuated, as by ultraviolet light. It is improbable that a true interfering effect can be produced by an inert " dead " virus.

When injections of live or irradiated vaccine are given after infection it is probable that the bulk of the fixed virus in the vaccine is absorbed into the blood and reaches the central nervous system. Here the virus particles "occupy " susceptible nerve cells, and may produce some histological changes (see below). When the street virus, ascending slowly along nerve tracts, reaches the central nervous system it finds the cells it would normally infect already occupied. Hence no infection can be initiated. It is probable that the street virus is not actually destroyed by the interfering agent, and may remain " latent " for a period, perhaps to give rise to symptoms of rabies after a long interval.

It is difficult to see how " killed " particles in, for example, Semple's phenolized vaccine can act as interfering agents, unless, as suggested above, some reactivation occurs in the tissues.

In support of the suggestion that the interference phenomenon may operate is the fact that definite lesions occur in the central nervous system of animals vaccinated by the Pasteur method (NICOLAU *et al.*, 1931 ; CRUVEILHIER *et al.*, 1935). These lesions have been attributed to a mild infection by the attenuated virus. Thus there is some cellular infiltration, and satellitosis of nerve cells. Further, LÉPINE and SAUTTER (1938) found nuclear inclusions in brain cells after vaccination with phenolized virus, and attributed these to the presence of living virus in their vaccine.

At this point it may be of interest to refer to certain work carried out with bacteriophage, which has recently been reviewed by DELBRÜCK (1946). Although the precise biological position of this agent is obscure, it is evident that it has many properties resembling those of animal viruses. When attempts

were made to grow two different phages simultaneously on one host, it was found that, depending largely on the timing, one of the two agents was excluded from growth. This phenomenon is known as " mutual exclusion ", and appears to resemble closely that of " interference " discussed above. Mutual exclusion took place between related as well as unrelated phages. It was found that the excluded virus might greatly lower the yield of the excluding virus. Exposure to ultra-violet light caused a marked drop in the infectivity of phage, but such irradiated material could still produce the excluding effect.

Delbrück suggests that the evidence at present available is compatible with the assumption that the entry of the first phage particle into the bacterial cell causes the cell membrane to become impermeable to other particles.

Attention may also be drawn to the phenomenon of superinfection described by MAGRASSI and others in infection with the virus of herpes febrilis (MAGRASSI, 1935, 1935–6 ; DOERR and SEIDENBERG, 1936–7 ; HALLAUER, 1937 ; DOERR and KON, 1937). It was found that if the rabbit cornea was inoculated with an encephalitogenic strain of herpes, virus travelled to the brain in 3–4 days. If at about this time an intracerebral injection of virus was given, no encephalitis ensued, either from this injection or as a sequel to the herpetic keratitis. Apparently the two doses of virus " cancelled " each other. A similar cancellation of infectivity could be achieved if the first injection was given intradermally, and the second intracerebral injection after about 7 days. Interference in both cases could be brought about only if the second injection was given intracerebrally. In this connexion some work of PUNTONI (1921) may be recalled. This worker infected rabbits subdurally with street virus, and during the incubation period administered fixed virus intravenously. He found that cancellation occurred and the animal remained in perfect health.

It is evident that no definite opinion can yet be expressed on the mode of operation of anti-rabies treatment, and it is suggested that at present the interference phenomenom offers the most likely explanation.

Anti-rabies Treatment in Man.

Types of vaccine used.—Vaccines used in anti-rabies treatment can be classified into two main types—attenuated or killed. Pasteur's original method, in which living but attenuated *virus fixe* is used, is still widely employed in France and her colonial Empire. A modification of this method involves the use of glycerol as an attenuating agent.

Another method is that known by the name of Hoegyes, in which serial dilutions of live *virus fixe* are made, the course comprising injections of gradually increasing strength.

Another method of securing attenuation is by heating virus suspensions to a point below the thermal death point.

Certain chemicals, particularly phenol, chloroform, ether and formol, inactivate virus if left long enough in contact, and if used in a sufficient concentration. These agents may take several days to destroy the virus ; certain chemical vaccines may contain small amounts of live virus, for example Puntoni's and Fermi's phenolized vaccines, and Alivisatos's etherized vaccine. In the well-known Semple type of vaccine as used in India, the virus is inactivated, and the preparation cannot be shown to contain virus in a state capable of initiating the characteristic clinical syndrome of rabies in susceptible animals.

Formolized vaccines are also used in human anti-rabies treatment, but the chloroformized type is employed chiefly in veterinary work.

Serotherapy in human anti-rabies treatment.—Serum therapy combined with anti-rabies vaccination has been used in human treatment, with somewhat encouraging results (SHORTT *et al.*, 1934–5 ; PROCA and BOBES, 1940).

Proca and Bobes refer to the fact that in those cases that develop rabies despite treatment the incubation period may be considerably prolonged, as if serum inhibits but does not completely destroy the virus. It is probable that the anti-rabic sera used could be improved and rendered more strongly rabicidal. The experimental work of Habel (1945) referred to above is most promising, and it may be that, in the future, serotherapy will play an important rôle in anti-rabies treatment, in combination with the use of potent vaccines.

Administration of vaccines.—Anti-rabies vaccines are usually given by the subcutaneous route, daily for 10–21 days, beginning as soon as possible after the bite. The course of treatment is graded according to the degree of risk judged to exist. Thus, persons who have only been licked or scratched receive a less intensive course, whereas those bitten on the face receive intensive treatment.

Anti-rabies treatment by the Pasteur or other method involving the use of attenuated virus must be administered in a central anti-rabies institute, owing to the elaborate technique required to maintain the doses of graded virulence. Chemical vaccines can, however, be given in out-stations. There has been much discussion of the value of this decentralization of treatment. On the one hand, patients are spared much unnecessary travelling to a central institute, and the treatment can be begun much more promptly. On the other hand, there is a tendency for patients to be treated who are not, in fact, at risk from rabies. These out-stations are usually in the charge of part-time officers, who may naturally be reluctant to refuse treatment, whereas a whole-time director of a central institute would probably not hesitate to refuse treatment to a patient thought not to be at risk. It is believed that a large proportion of the persons treated year by year at out-stations are not at risk from rabies. Consequently, the figures for deaths from rabies following treatment are fallaciously low, for many treated persons are virtually normal people. The same "dilution" effect applies to all statistics relating to mortality after anti-rabies treatment, but is probably less pronounced in the case of central institutes.

Indications for anti-rabies treatment.—Anti-rabies treatment should be started immediately when a person is bitten or scratched under the following conditions (Johnson, 1943):—(1) If the biting animal is clinically rabid; (2) if the animal is proved rabid by laboratory tests; (3) if the animal is suspected of being rabid; (4) in endemic areas after the bite of a stray animal that escapes; (5) after the handling of animals diagnosed as rabid, and if fresh abrasions of the skin have been contaminated with saliva.

The amount of treatment depends on the degree of risk. For example, in India, with phenolized vaccines, those least at risk receive 2 cc. daily for 7 days, and those most at risk receive 10 cc. daily for 14 days (Webster, 1944).

The mode of operation of human anti-rabies treatment.—The rationale of anti-rabies treatment has already been fully discussed above, as practically all the relative information has been derived from animal experiment. It may be noted that Busson (1930) found Negri bodies less commonly in persons dying of rabies after anti-rabies treatment than in untreated persons. It is suggested that the mechanism of protection may be one of interference between the particles of the fixed virus in the vaccine and the street virus.

Death from rabies after treatment.—Despite the exhibition of anti-rabies treatment, a number of patients nevertheless die of hydrophobia. Anti-rabies treatment is most likely to fail in the case of severe wounds, wounds on the head and face, wounds from wolves or jackals, and when it is started after a delay of several days. It must be realized that in certain countries it is extremely difficult to get an accurate record of the number of cases of rabies developing after treatment, particularly as the illness may develop when the patient has

returned home. This incomplete " follow-up " of cases constitutes another serious factor complicating the evaluation of anti-rabies treatment.

McKendrick (1940) for many years analysed the statistics, relating to death in treated persons, furnished by practically every Pasteur Institute in the world. Before his death he analysed figures relating to over one million treated persons. McKendrick was primarily concerned with determining the relative efficiency of the dozen or so more commonly used methods of treatment, and assumed that treatment was in fact an effective means of preventing rabies. He did not discover any definite superiority of one vaccine over another. Unfortunately, it does not now appear to be possible to use this remarkable series of figures to help in evaluating anti-rabies treatment in general, rather than any one method in particular. Nevertheless, McKendrick has furnished some extremely important information that does to a certain extent help in this respect. For the dozen or so years covered by his reviews the over-all mortality from rabies in treated persons was 0·33 per cent. This mortality rate was seen to be influenced by various factors.

The race of the treated person was the most important single factor. Over the whole period covered by the reviews the mortality in Europeans was 0·15 per cent., while in non-Europeans it was 0·56 per cent., about four times as high. It seems unlikely, however, that this is due to a true racial susceptibility of the non-European. It is more likely that the proportion of non-Europeans treated by anti-rabies treatment, and who are genuinely at risk, is higher than in the case of Europeans. Further, Europeans are usually bitten through clothing, which has the effect of absorbing the infective saliva.

The mortality was considerably higher in the case of bites on the head, face and neck.

Deeper wounds were more fatal than superficial wounds.

Bites from wolves carried a mortality in treated persons of 6·78 per cent., as against 1·31 per cent. for jackal bites and 0·26 per cent. for dog bites.

Wounds on bare skin were more fatal than those inflicted through clothing. In fact, as in the case of untreated persons, the more virus inoculated into the wound, and the more extensive the trauma, the less effective is anti-rabies treatment seen to be.

An extraordinary point brought out in McKendrick's reviews is the effect of lateness of arrival for treatment on the death rate. It might be supposed that if anti-rabies treatment is a form of active immunization, then the earlier it is started the better. On the contrary, there appeared to be no danger in postponing treatment for up to 14 days from the bite. In the case of Europeans, treatment started even after the 14th day carried no further increase in mortality, although in non-Europeans there was a striking increase in mortality after this period. Again, it may well be that the true explanation of this apparent discrepancy lies in the question of the incidence of persons genuinely at risk. It is difficult to see otherwise why one race can apparently delay treatment with impunity and the other cannot.

The actual figures were as follows :—

Time of commencement of treatment, days after bite	Mortality percentages		Ratio of mortality in the two races European/non-European.
	European	non-European	
0– 4	0·19	0·47	1 : 2·5
5– 7	0·10	0·47	1 : 4·7
8–14	0·07	0·50	1 : 7·1
Over 14	0·12	1·08	1 : 9

The value of human anti-rabies treatment.—It is desirable at this stage to list *seriatim* the more important of the factors, discussed above, that complicate any evaluation of anti-rabies treatment of man :—

(1) The mortality from rabies in untreated persons bitten by rabid animals is on the average no more than 15 per cent., and may well be less. The mortality rate varies directly with the amount of virus inoculated into the wound, and with the extent of trauma to the tissues. Strains of street virus probably vary in virulence and possibly also in antigenic structure.

(2) After infection, rabies street virus spreads to the central nervous system by nerve paths, but the minimal infecting dose is not known. Nor is it known how long the virus takes to reach the central nervous system. In certain circumstances virus can apparently remain latent in the body and cause symptoms after a prolonged incubation. It may be that the virus can remain latent in tissues other than those of the nervous system, for instance in the salivary glands.

(3) Cauterization of bites has been shown experimentally to be effective in preventing rabies. The treatment is obviously of some value in man.

(4) Animals can be actively immunized, by courses of vaccine, to withstand a subsequent " challenge " dose of test virus injected intracerebrally. Some phenolized vaccines have been shown to be relatively ineffective in this respect, but chloroformized and irradiated vaccines are much more potent. Irradiated vaccines probably contain some living virus in an attenuated form.

(5) It is difficult to prevent rabies developing by injections of vaccine given after infection, but this has been secured by certain workers using potent vaccines in small laboratory animals.

(6) A number of phenolized vaccines tested in the U.S.A. have been shown to be almost inert in inducing active immunity in laboratory animals.

(7) Strains of *virus fixe* vary considerably in their immunizing potency. Immunizing potency is not a constant feature of any given strain and should be checked from time to time. Some strains have been found to be very feebly antigenic.

(8) In the past a considerable number of persons must have been treated with vaccines of very low, or no, immunizing potency.

(9) The most potent type of vaccine—brain tissue irradiated by exposure to ultra-violet light—has not yet been generally used in human treatment.

(10) The mode of operation of anti-rabies treatment is not known, but is either due to neutralization of the virus by antibodies, or to neutralization produced by the interference phenomena.

(11) Large numbers of persons are treated with anti-rabies vaccines who are not at risk from rabies. The result of this is that the figures for mortality from rabies in treated persons are fallaciously low. Further, owing to difficulties of " follow-up ", numbers of deaths from rabies in treated persons do not appear in the statistics.

(12) It is only very rarely possible to tell whether any given treated person has actually been infected with rabies virus or not. The fact that the biting animal is proved rabid does not mean that virus has been deposited in the patient's wound.

(13) McKendrick's reviews do not point to the superiority of any one type of commonly used vaccine.

(14) Mortality from rabies after treatment depends on the quantity of virus inoculated by the biting animal and the amount of trauma caused. According to the figure of McKendrick, non-Europeans are nearly four times as susceptible as Europeans, but, as remarked above, this is probably not a genuine racial difference.

(15) Lateness of arrival for treatment, especially in Europeans, does not appear to affect the mortality rate adversely, although owing to the question of varying risk, too much attention cannot be paid to this point.

It may appear, therefore, that there are so many variable factors that any accurate appraisal of anti-rabies treatment in man is impossible. Nevertheless we know that anti-rabies treatment can act in small laboratory animals, even when applied after infection, and there seems to be every justification for expecting some benefit from the treatment in man.

Surprisingly few papers have been published in recent years bearing on the value of anti-rabies vaccination in man, under circumstances in which adequate control untreated groups have been observed. CORNWALL (1923) stated that the only way to evaluate anti-rabies treatment is to take those instances in which a presumably rabid dog has bitten several persons, some of whom are treated and some are not. Both groups must be observed for several months. He gave the following figures from S. India :—

Total number of persons observed	2,174
Number treated	812
Deaths among treated	2·9 per cent.
Number untreated	1,362
Deaths among untreated	6·2 per cent.

Cornwall therefore concluded that treatment saved one out of every two who would otherwise have developed hydrophobia. These results are highly unlikely to have arisen by chance. It is not, of course, possible to be certain that the persons in the two groups were at the same degree of risk, but this can reasonably be assumed.

YU (1941), in China, observed 201 patients fully vaccinated after dog bites, of whom 9 died, giving a case mortality rate of 4·5 per cent. In two of these, however, treatment was started late. In 182 unvaccinated persons there were 18 fatal cases of rabies, giving a mortality of 10 per cent.

Taking both these sets of figures at their face value, the mortality in treated cases would seem to be about half of that in untreated cases. It will be observed that the figures for mortality in these two treated groups are considerably above the figure for mortality from dog bites in treated persons given by MCKENDRICK (1940), namely 0·26 per cent. The dilution by cases not at risk in McKendrick's series, as well as incomplete " follow-up ", probably accounts for much of this discrepancy.

In an attempt to obtain further information I communicated with M. REMLINGER, who has studied rabies for a life-time ; he kindly sent me a detailed personal communication along the following lines : Let us consider 1,000 persons treated in an anti-rabies institute for dog bites. Probably only 500 of these have been bitten by rabid dogs. As the death rate in such persons may be 15 per cent. we may expect 75 of the 1,000 persons to die of rabies if untreated. The mortality in treated persons is, however, only about 5 per 1,000. By this line of argument it appears as if anti-rabies treatment saves 70 persons per 1,000 treated.

I question, however, whether in many institutes nearly as many as 500/1,000 treated persons are actually at risk following dog bites. Suppose we regard the number at risk as 100, and the mortality in untreated cases as 10 per cent., then we arrive at a figure of only 10 persons dying in our group of 1,000 *without any treatment.*

It does not, therefore, seem to be possible to put forward a strong case in support of anti-rabies treatment if one argues on general lines, rather than from figures of controlled series such as that of Cornwall, owing to the numerous variable and unknown factors.

When we come to discuss the position in the much severer wolf bite, there seems to be more satisfactory evidence of the value of treatment. The mortality from untreated wolf bites, due to rabies, is generally believed to be not less than 60 per cent., and it is said to be very rare for wolves to bite unless rabid. Accordingly, of 1,000 persons bitten by wolves, practically all may be considered to be genuinely at risk, so that not less than 500–600 of the 1,000 should die from rabies if untreated. Yet the mortality from rabies in treated cases of wolf bite is not more than 15 per cent. (REMLINGER). If one accepts the high mortality in untreated cases, it would appear that anti-rabies treatment is of definite value. Even there the question of dilution by cases not at risk must be considered. Personally, I am somewhat sceptical about the degree of risk in persons bitten by wolves. It seems likely that wolves may bite man from causes other than rabies, such as hunger.

Professor LÉPINE of the Institut Pasteur also wrote to me expressing his firm conviction in the value of anti-rabies treatment, not only in wolf-bites, but also in dog-bites, and quoted a number of instances of its apparent effectiveness.

In conclusion, I suggest that on the evidence at present available, it is justifiable to continue to regard anti-rabies treatment as being of some value in the prevention of rabies, although it may not necessarily act by the orthodox process of active immunization. There is no justification for withholding treatment from persons thought to be at risk. The treatment as at present employed could probably be considerably improved, partly by the greater use of immune serum, and partly by the greater use of more potent vaccines. The vaccines found to be most effective in animal experiments are not yet generally used in human treatment. There is a wide field for further research, particularly into the mechanism involved in the acquisition of the immune state. It is most desirable that every effort should be made to secure statistical evidence concerning the value of anti-rabies treatment, by comparing the incidence of the disease in treated persons, and in those exposed to the same risk who, for some reason, have not taken treatment.

Summary.

1. The experimental basis of anti-rabies treatment has been examined and recent observations have been reviewed.

2. Provided that potent vaccines are used, it has been shown that experimental rabies can be prevented by injections given before, and in certain circumstances after, infection.

3. The mechanism underlying the prevention of rabies by anti-rabies treatment administered after infection in man and animals is obscure. It may be that anti-rabies immunity of this type is an example of the interference phenomenon.

4. The main factors that render the evaluation of human anti-rabies treatment so complicated have been discussed.

5. It is concluded that anti-rabies treatment is of some value in the prevention of rabies, but that improvements could be effected, such as the use of serotherapy and more potent vaccines.

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SUMMARY OF RECENT ABSTRACTS.*

IX. LEPROSY.

Epidemiology.

JUON (p. 389) contributes an interesting note on a small focus of leprosy which existed up to 1927 in Switzerland. Two groups of people were involved, and in each group there was a strong family history of the disease.

DHARMENDRA and SANTRA (p. 738) review the results of leprosy surveys made by the latter in various parts of India. The incidence varies considerably, from 0·17 to 6·64 per cent. of the population in different parts ; the incidence of lepromatous disease varies from 0·1 to 0·96 per cent., providing from 5 to 62 per cent. of the total cases. A high total incidence is usually associated with a high incidence in children, and of lepromatous cases. The proportion of infected children varies greatly. The authors make the point that in some areas patients with advanced disease are isolated in their own homes or in huts outside the villages, and that where such measures are customary, a high lepromatous rate tends to be associated with a low gross incidence and a low child rate. This indicates that such measures help to control infection ; the tendency should be encouraged.

In the Annual Report of the Indian Council of B.E.L.R.A. for 1944 (p. 1005) the same point is made, that a comparatively high lepromatous rate may be accompanied by low gross incidence and a low child rate, in areas where some kind of isolation is practised.

In the annual report of the Madras Provincial Council of B.E.L.R.A. (p. 290) it is stated that village surveys have shown a gross incidence rate of 2·47 per cent., and a child rate of 2·68 per cent. ; these are very high. There are great variations in the infectivity rates in different villages. A reduction in child infections has followed night segregation of infective patients in villages, by which means contact with susceptible children is reduced. It is estimated that 5,000 to 7,000 persons with leprosy are living in Madras city, of whom some 10 per cent. are probably infective.

An account of leprosy in the Tehri Garhwal State, United Provinces, India, is given by SANTRA (p. 393). A survey showed an incidence of 2 per cent., and a high proportion of cases are infective. SHAMA RAO (pp. 393, 1005) reports on leprosy surveys in Hyderabad, where incidence varies from 0·24 to 0·36 per cent., and where 31 to 43 per cent. of the cases found were lepromatous.

MUIR (p. 390) has paid return visits to Antigua, St. Kitts and Nevis, and Jamaica, and reports on the progress made, in relation to leprosy, since his first visit. These reports are primarily of local interest. VAN DER SAR (p. 391) gives an account of the history of leprosy in the Dutch West Indies.

Leprosy surveys in Bolivia have shown an incidence rate of 0·07 per cent. SUAREZ (p. 813) shows that the foci are active, stationary, or in the process of becoming extinct. Of the cases found, the great majority were in males of middle age. Various measures are being taken for treatment and contact examination.

MUIR (p. 1004) has given an account of the past work of B.E.L.R.A. and outlines plans for future work in the Colonies.

Aetiology.

DAVISON (p. 295) has found *Myco. leprae* in scrapings from the nasal mucosa in cases of nerve leprosy, but only rarely in material from incision of a macule.

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* The information from which this series of summaries has been compiled is given in the abstracts which have appeared in the *Tropical Diseases Bulletin*, 1945, v. 42. References to the abstracts are given under the names of the authors quoted and the page on which the abstracts are printed.

He makes the point that smears should be stained for 20 minutes in warm fuchsin and decolourized for 20 minutes in 5 per cent. sulphuric acid. If these times are reduced there is a danger that diphtheroids may retain the stain and be mistaken for *Myco. leprae.* By using a triple stain, ALEXANDER-JACKSON (p. 899) has demonstrated non-acid-fast forms of *Myco. leprae* in nasal smears and in skin of leprosy patients. Zoogloeal and spore-like forms were also apparently demonstrated.

DHARMENDRA and MUKHERJI (p. 900) have failed to infect splenectomized monkeys by intraperitoneal injection of clippings from the skin of lepromatous patients. They have therefore not confirmed previous work by others who have claimed success by this method.

DE SOUZA-ARAUJO (p. 132) has cultivated strains of acid-fast bacilli from groups of ticks of various species, which had been allowed to feed on leprosy patients, and which had subsequently been triturated and inoculated on to Loewenstein's medium. He considers these pigmented organisms to be *Myco. leprae*, and from them has prepared leprolins for use in intradermal tests. These have been compared with lepromin in a series of tests carried out by MARIANO (p. 133); there was considerable difference in the results.

DE SOUZA-ARAUJO (p. 1006) has infected white rats by infecting them subcutaneously with emulsions of the glands of a patient with leprosy, which were rich in *Myco. leprae.* From some of the organs of the rats he succeeded in cultivating chromogenic acid-fast organisms. He (p. 1006) has also cultivated on Loewenstein medium, acid-fast organisms from pus taken from a fluctuating leprotic lesion of a boy. When these cultures were injected into animals, they caused abscesses in the axilla, peritoneum and elsewhere, but smears from the viscera were negative.

GRAU TRIANA (p. 212) claims to have cultivated leprosy bacilli on modified Petragnani's medium to which, at the time of sowing, 10 drops of a solution of oxidase from potato, with or without 10 drops of a solution of ferrous sulphate, are added. The reasoning which led to this method is that in media sterilized by heat such ferments are destroyed, but that the tubercle bacillus can grow because it supplies its own ferments, whereas the leprosy bacillus is deficient in oxidase. The author states that colonies begin to appear in 5–7 days. In a second paper GRAU TRIANA *et al.* (p. 213) give details of several media used on these lines.

TROUT (p. 900) has cultivated an acid-fast organism from lepromata, on a Difco agar medium over which CO_2 was passed during incubation.

IGNACIO CHALA and LLERAS RESTREPO (p. 566) have studied 6 strains of acid-fast bacilli isolated from leprosy lesions in man, by inoculation into animals, and have made a detailed account of the lesions provoked. Complement-fixation reactions were tested with certain well-known strains, and in a minority of cases positive results were obtained.

Pathology and Clinical Findings.

PARMAKSON (p. 295) has made careful histological examinations of the skin in various types of leprosy. He concludes that active skin lesions in nerve leprosy are characterized by tuberculoid changes, but that these changes do not occur in lepromatous leprosy. In clinical nerve leprosy, lepromatous changes are not found. If a change from one type to another occurs, the typical appearances of the one disappear before those of the other arise. The Mitsuda reaction is usually negative in lepromatous leprosy, and positive in nerve leprosy.

CERRUTI (p. 567) made a detailed study of biopsy material taken from the nasal septa in leprosy, and points out that some of the pathological changes may be found in patients who, clinically, appear to be normal. This kind

of examination may therefore be useful and important in early diagnosis, and especially in contacts.

Mestre Miyares (p. 43) classifies leprosy as lepromatous, tuberculoid or non-specific. The first type is infective, the second not, and the third may remain true to its form (the neural type) or may pass to either of the others.

de Souza-Araujo (p. 1010), on the other hand, thinks that the division of leprosy into lepromatous, tuberculoid and macular types is artificial, and that all forms are mixed. By examining the cutaneous lymph in " tuberculoid " cases he has found small granules and coccobacillary forms of the organism, and thinks that relapses in apparently burned-out cases are due to development of these forms.

Ibarra Perez and Gonzalez Prendes (p. 1009) note that in children separated from leprous parents there is usually a silent interval, lasting up to 5 years, before signs of leprosy appear in them. They have analysed the initial lesions seen in a large number of cases of leprosy. These were macular in 37·9 per cent., but areas of anaesthesia, infiltration of the ears, systemic disturbance with fever, and rhinitis were the first signs in smaller percentages. Most of these early lesions were on uncovered parts of the skin. The authors think that the nose is not the portal of entry, but rather the portal of exit of the organisms. Examinations of the placental tissues, umbilical cord, blood from the cord and from the infants themselves, in a series of 16 newly-born children of leprous mothers, were made by Trespalacios and Jover (p. 212), with completely negative results for leprosy bacilli.

de Souza (p. 567) reports a case of leprosy in which ptosis, enophthalmia and myosis were present, possibly due to leprosy. The syndrome is well known, but is usually the result of other conditions.

Argüelles Casals (p. 568) describes a case in which exquisite tenderness of the finger tips and nails was present, along with leprosy. He does not argue that leprosy was necessarily the cause of this condition.

Degotte (p. 295) has investigated the question of the infectivity of neural leprosy in the pygmies of the Belgian Congo. On the whole he thinks that such patients are, at times, infective.

Changes in the euglobulin-tyrosin and the albumin-globulin ratios in leprosy are attributed by Ross (p. 297) to hepatic dysfunction and to liver damage.

Lepromin : Other Tests.

At the Leprosy Research Department, School of Tropical Medicine, Calcutta (p. 739), further research has been done by Dharmendra on the antigens of the leprosy bacillus and other acid-fast organisms. The acid-soluble fraction of all these is active, giving positive reactions in neural leprosy and negative reactions in lepromatous disease. The fact that one of the tested organisms (Kedrowsky's) is easily cultivated will greatly simplify the production of an antigen of value in prognosis.

Bechelli *et al.* (p. 900) have tested with lepromin persons (in New York) who have never been in contact with leprosy. Some positive results, both delayed and early, were given. They found that the early reactions were given, in 35 of 36 tested, by people positive to tuberculin, and think that infection with the tubercle bacillus may account for this result.

Rotberg (p. 568) produces convincing evidence to show that leprosy patients negative, or weakly positive, to lepromin are much more likely to develop serious reactivation of the disease than those who give strongly positive results. If this fact were appreciated, the preventive medical services could concentrate more actively on following up the negative and weak reactors, who are prone to relapses of infective type. Fernandez (p. 471) makes the point that, in an infected person, a positive reaction to lepromin indicates good resistance, and a

good prognosis. A negative test in such persons is an indication that careful observation is needed, and it is advisable to start treatment; prognosis should be guarded. The same author (p. 297) has found that non-leprous persons can be rendered sensitive to lepromin by intradermal injection of suspensions of *Myco. leprae*, or of tubercle bacilli. The early reaction to lepromin (due to the protein fraction of *Myco. leprae*, and to be distinguished from the late, Mitsuda, reaction) can be attributed to previous sensitization by leprosy or tubercle bacilli.

Mom and Basombrio (p. 1012) have continued their work on lepromin and 2–4 dinitrochlorobenzene, and now report that intradermal injection of each of these substances gives reactions which, in the majority of cases, are remarkably concordant. There are few cases in which they are contradictory. The injections may provide early or late reactions, and these tend to be negative in lepromatous leprosy and positive in tuberculoid and "non-characteristic" cases.

de Souza-Araujo and Miranda (p. 1007) found that ticks fed on leprosy patients may take up leprosy bacilli, and that from these ticks acid-fast organisms can be cultivated. Similar findings are recorded by de Souza-Araujo (p. 1007, 1008) in the case of triatomid bugs, certain mosquitoes, sandflies, simuliid flies and leeches, but not in the case of *Cimex lectularius*. The same author (p. 1008) has cultivated the acid-fast organisms taken up by these insects, and has obtained 7 cultures, one from the original patient, the remainder from ticks and triatomid bugs. He and his colleagues (p. 1009) have attempted to transmit leprosy to man by the bite of infected triatomid bugs, but the results were indefinite [partly, perhaps, because the persons whom it was intended to infect were burned-out leprosy patients].

A somewhat similar experiment was carried out by de Oliveira Castro and Mariano (p. 1009) but with mosquitoes instead of bugs. After the infected mosquitoes had bitten patients with burned-out leprosy, acid-fast organisms were found in the connective tissue spaces near the bite, but there remains the possibility that they were there before the experiment was made.

de Souza Araujo (p. 1010) describes his method of preparing lepromin from lepromata, by emulsification and addition of phenol. Mariano (p. 1010) has tested 5 of the leprolins prepared by de Souza Araujo, three of them were derived from cultures of acid-fast organisms from ticks (see above). He compared the results of tests with these leprolins, with results given by lepromin, and found a considerable degree of agreement, though there was some variation between the different leprolins. Miranda (p. 1011) has done similar work, with similar results. In general, these leprolins tend to give negative reactions in lepromatous cases and positive reactions in nerve leprosy.

Balagangadharan (p. 739) brings evidence which supports the view that the Kahn reaction is quite often positive in leprosy in the absence of syphilis. Eccles and Ross (p. 297) state that the Mazzini flocculation slide test, though not so sensitive in leprosy as the Kolmer and Kahn tests, has the advantage of greater simplicity.

Treatment.

At a Conference held at the Pretoria Leper Institution (p. 292) Drewe referred to the value of rest and good food in the treatment of leprosy. Davison defined the criteria of cure which should be applied before patients are discharged from hospital. He also discussed the kind of leprosy institution which would be suitable for South Africa and other countries with a similar incidence of leprosy, and the question of compulsory segregation, of which he approves in certain conditions. Moiser showed that conjugal infection in Southern Rhodesia was low, 1·57 per cent., and referred to the possible transmission of the disease by cockroaches. Thornton noted that at the institution for leprosy in the

Transkei, 27·3 per cent. of patients had been discharged during the past 10 years; in some of these recrudescence had occurred.

No benefit from the use of pooled plasma transfusion was noted by FAGET and POGGE (p. 297) in the treatment of leprosy. It was thought that this treatment might prove valuable in the hypoproteinaemia and nephritis of leprosy, but the results were disappointing.

SHAMA RAO (p. 393) describes a simplified method of preparing iodized *Hydnocarpus* oil; for details the original abstract should be consulted. DEGOTTE (p. 394) could not obtain chaulmoogra oil in the Belgian Congo during the war, and experimented with an oil obtained from a common plant, containing citronella. The results of treatment with this oil were reasonably satisfactory. ROIG and RODRIGUEZ DE LA CRUZ (p. 214) discuss the oils of the Cuban Flacourciaceae.

COT LESMES (p. 44) has used diphtheria toxoid in the treatment of leprosy, and reports favourably on the results, especially in lepromatous cases. This finding is in contrast with much of the more recent work on the same lines, and with the opinion of TIANT (p. 45) who thinks that this form of treatment shows little promise. He considers leprosy to be curable by general measures of improvement of health and by the use of chaulmoogra oil in high dosage.

DOS SANTOS NEVES (p. 472) has treated a few patients with vitamin A and a cholagogue, with satisfactory results.

Penicillin is apparently useless in the treatment of leprosy (FAGET and POGGE, p. 646).

ALLER ATUCHA (p. 902) writes strongly in favour of local applications of sulphathiazole in leprosy; the drug, either as a 15 per cent. jelly, a 10 per cent. suspension in oil, or a 15 per cent. watery emulsion, is applied to the skin after it has been scraped, or to ulcers. Lesions of the eye may also be treated with these preparations, and treatment with injected sulphathiazole, along with injections of chaulmoogra oil, is apparently useful for generalized lesions.

In trials of sulphanilamide, given by injection, in rat leprosy, CHORINE and CHABAUD (p. 298) have failed to find evidence of any effective therapeutic action, but local application of sulphanilamide in the treatment of ulcers and burns in leprosy, and treatment of the ocular lesions (keratitis, irido-cyclitis, etc.) with a preparation of sulphanilamide, have given encouraging results in the hands of CHORINE (pp. 298, 1013).

AMENDOLA (p. 901) has had satisfactory results, in ocular leprosy, from extirpation of the lachrymal gland. This is not surprising if the glands themselves are infected, but the author has also seen benefit even when the glands showed no evidence of disease.

SAGHER (p. 740) has used grenz rays in the disfiguring lesions of leprosy, with some success.

AMENDOLA (p. 901) discusses tracheotomy in leprosy, pointing out that it is not usually an emergency operation. The low operation is to be preferred, but there may form a thick muco-membranous exudate below the cannula, which is difficult to remove and which may necessitate a second, urgent, operation for its removal.

Arguing that the cause of perforating ulcer of the foot in leprosy is occasioned only by the loss of sensation, and consequent inattention to any wound, SILVEIRA (p. 473) states that ordinary treatment is effective. KIRKALDY-WILLIS (p. 740) has performed arterial sympathectomy to promote healing of an ulcer of the foot in a leprosy patient.

Institutions: Control.

BURGESS (p. 298) estimates that, throughout the world, no less than 15,000,000 people are affected by leprosy, either directly by the disease or because they are

dependants of infected persons. He proposes a world federation of communities of infected persons, which should be largely self-supporting through organized employment, and in which provision should be made for the families, infected or not. [The conception of communities in which these people should not be penalized because of a disease for which they are not responsible, is growing. These organized communities would not only offer a solution to the troubles of the infected, they would also help, perhaps more than anything else, to eradicate the disease, but they should be attractive.]

Davey (p. 1013) reports on the work done in the Owerri Province of Nigeria, where, in a population of 2,000,000, there are probably 75,000 persons suffering from leprosy. Some 18,500 patients have been brought within the scope of the leprosy work directed from the great leper colony, and they are cared for either in the central settlement, or in the 27 special villages, or at over 40 out-patient clinics. Repeated surveys are made and developing cases are discovered and treated while they are in a stage at which treatment is most likely to succeed. There are 20 leprosy inspectors at work in different parts of the Province, and their duties include the examination of contacts of infective persons. Already, in six areas, and with the cordial cooperation of the people themselves, practically all infective patients are isolated, and receive treatment. In these areas progressive diminution of the incidence of leprosy may be expected. The work has largely been financed by B.E.L.R.A., but the Nigerian Government has now taken it over, with the object of extending its scope.

The work of the Oji River leprosy settlement in Nigeria has progressed in spite of the war, and Money (p. 392) states that in 1943 there were 1,187 in-patients. There is a special compound for children. In the surrounding country there are several out-patient clinics at which treatment is given; in the whole Province there are 20,000–25,000 active cases, of which 3,000–5,000 are infective. Many of these are segregated in leprosy villages, but many more are isolated in their homes.

In the Belgian Congo compulsory segregation of leprosy patients is not advised, but Zanetti (p. 741) states that numerous agricultural villages are being organized, each to provide for 300–400 cases. These are visited each week by a medical officer. Isolation in these villages is more or less voluntary, but some mild pressure is applied.

Densham (p. 392) reports on a settlement recently started in Northern Rhodesia.

Cochrane (p. 291) discusses the whole question of leprosy control, especially in relation to the Madras Presidency. He advocates surveys of the different communities, night segregation of infective persons in their homes, and villages to lessen the infection of children. Institutions should be provided by all municipalities, and special sanatoria for children, because they cannot be isolated at home. Child contacts should be examined periodically. The Madras Public Health Act is being modified in this sense. No success can be expected unless a well qualified medical officer is placed in charge of the campaign in each province.

Sen (p. 1014) refers to a home for leprosy patients which has been founded in India and which is financed partly by private subscriptions and partly by grants from local authorities; it is the first of its kind to be supported in this way by the people themselves. He remarks that many of the inmates had been driven from their homes by their relatives. The home now contains some 300 patients; if similar undertakings were initiated elsewhere, some solution of the problem of begging lepers in India might be found.

Austin (p. 736) has written an account of the Central Leper Hospital, Makogai, Fiji. This is very well equipped for treatment, and the patients are also employed in certain industries. In recent years 40 patients per annum

have been discharged, with only 10 per cent. of relapses. Isolation is compulsory but the conditions are so favourable for the inmates that compulsion is regarded as successful. An account of the work of this hospital during 1943, is given by the same author (p. 294) ; this cannot further be summarized. This institution is very progressive.

Hopkins and Faget (p. 737) have analysed the cases admitted to the National Leprosarium at Carville between 1928 and 1944. Admissions of patients from Texas have increased, and the disease is still endemic in some of the southern States and Mexico, though it is declining in the foci in Massachusetts and Minnesota. There are still many white patients, some of whom are soldiers infected during various wars. A family history of leprosy is not uncommon, where it can be obtained, but conjugal infection is rare. The authors believe that the Kolmer and Kahn tests may be positive in leprosy in the absence of syphilis. The duration of cases, from admission to death, varied from 9·3 years (lepromatous) to 14·5 years (neural) ; 145 of the 723 patients were discharged with arrested disease, and only 16 relapsed. Most of the discharged patients had neural or tuberculoid leprosy. Most of the deaths were due to nephritis, tuberculosis or leprosy.

Wharton (p. 737) describes the leprosy hospital at Mahaica, British Guiana ; from this institution a programme of contact examination is being conducted. As a result of examination of children, a number of early cases have been detected.

Sloan (p. 296) claims that the policy of compulsory segregation has been effective in Hawaii, and quotes the decline in incidence since 1890 in support of his contention.

Rat Leprosy.

Fielding (p. 903) has made a careful study of rat leprosy. He has demonstrated heavy infections of the stomach, and related these to the heavy excretion of leprosy bacilli in the faeces. Repeated inunction of the skin with emulsions of rat leprosy bacilli is capable of causing extensive invasion of the skin, and the bacilli have been found in those parts of the skin which come into contact with the ground, and therefore, potentially, with infective material. This creates a link between soil contamination and dissemination of the disease. The results of Fielding's work also indicate that rat leprosy bacilli from faeces, urine and primary ulcers are more virulent than those from granulomata and ulcers of long standing. For the production of superficial lesions there must be repeated inunction, or injection, of the organisms, and the use of bacilli of high virulence. In natural conditions infection is doubtless due to repeated contact with soil infected by faeces containing the organisms, but may also be carried by rat lice. Hookworm larvae can also introduce the bacilli, but faecal organisms introduced by the mouth failed to infect.

Linhares (p. 1014) discusses possible routes of infection in rat leprosy, and shows that he has been able to infect fowls by feeding them on rat leprosy material, or by injecting it, and pigeons by injection.

Dharmendra and Mukherji (p. 903) found that sulphapyridine, given by the mouth, had no effect on rat leprosy.

Charles Wilcocks.

MALARIA.

BIRRELL, N. V. **A Case of Indigenous Malaria in Northern Ireland.** *Brit. Med. J.* 1946, Apr. 27, 649–50.

A member of the W.R.N.S. with *P. vivax* malaria was admitted to hospital in Londonderry on July 16th, 1945. The author advances sound reasons for his belief that infection had been contracted locally. *A. maculipennis* [variety not named] was found breeding in the locality; there were numerous cases of malaria under treatment among members of the Services, and the spring of 1945 had been unusually mild. *Norman White.*

COLLINS, R. K. **Rural Malaria: its Epidemiology and Prevention. A Study.** *Türkische Ztschr. f. Hyg. u. Exper. Biol.* Ankara. 1941, v. 2, No. 2, 17–28. [Turkish version 5–16].

The author reports an outbreak of malaria in Sincanköy, Turkey, in a group of refugees who entered the area. *Anopheles maculipennis typicus* and *A. superpictus* were present. All three types of parasite were found, *P. malariae* being relatively common in the small series recorded. *Charles Wilcocks.*

DUKHANINA, N. N. [**Carriers of *Plasmodium vivax* in the North under Mass Chemoprophylaxis.**] *Med. Parasit. & Parasitic Dis.* Moscow. 1945, v. 14, No. 5, 63–76, 1 fig. [In Russian.]

Observations were made on the carrier-state in malaria (*P. vivax*) among the population of the Archangel Province, in northern U.S.S.R. [61–62° N. Lat.]. The special objects of the investigation—apart from the general characteristics of the carrier-state in the north—were the conditions under which infected persons become carriers, the effect of treatment, causes of repeated carriage, and density of parasites in carriers, as compared with that in persons with clinical symptoms.

In the village (Telegovo) selected for this investigation the highest percentage of carriers among the persons examined was 9 per cent. in 1939, the lowest 0·9 per cent. in 1940, while in 1941 there was not a single carrier, the decline being correlated with an amelioration of the epidemiological position. Carriers were found both among persons affected with malaria in the preceding and in the current year (12·6 per cent.), and among those who had no malaria but were equally exposed to infection (4·5 per cent.). In 73 per cent. of cases carriers were detected in the pre-epidemic period, and only 27 per cent. in the epidemic period. Among persons who had undergone drug prophylaxis, parasite-carriers made up 42–44 per cent. of the total number of cases of malaria. As a rule, the carriers were persons who had received insufficient drug treatment. The number of parasites in the blood of carriers is considerably lower than in acute cases, in 90 per cent. of cases not exceeding one parasite per field of the microscope. *C. A. Hoare.*

SOUTH AFRICA, UNION OF: **Malaria Areas in the Union of South Africa. A Map of the Malarial Survey by the Department of Public Health of the Union (in collaboration, in the case of Swaziland, with the Swaziland Administration) 1938.** 1941. Pretoria: Govt. Printer.

The scale of this map is 15·77 miles to the inch. On it are shown four areas:—

A. In which the risk of infection is continuous;
B. In which it is serious, and in which epidemics occur during summer;
C. In which a summer epidemic occurs each year, but of milder type;
D. In which epidemics occur occasionally.

Area A is found only in one district of the east coast, near the border of Moçambique. Area B covers the north and east of the Union, with Area C to the south and west of Area B. Area D lies again to the south and west of Area C, and reaches Pretoria, Witbank, Newcastle and Durban. The remainder (and greater part) of the Union is apparently not affected by malaria.

It is explained that the areas are only approximately correct. They are shown in 4 colours, and are very clearly marked. This is a useful map for the malariologist ; it measures some 3 ft. 8 in. by 3 ft. No price is quoted ; the map was produced for official purposes. *Charles Wilcocks.*

Muspratt, J. **Experimental Infection of the Larvae of** *Anopheles gambiae* **(Dipt., Culicidae) with a** *Coelomomyces* **Fungus.** [Correspondence.] *Nature.* 1946, Aug. 10, 202.

Carter, H. F. **Ceylon Anopheline Mosquitoes and Malaria.** *Ceylon Health News.* 1945, July–Sept., v. 12, No. 1, 5–8.

Ch'i Ho. **The Anopheline Fauna of Szechuan Province.** *Acta Brevia Sinensia.* 1945, No. 10, 1.

McArthur, J. N. **Malaria Transmission in Borneo.** *Lancet.* 1946, July 27, 117–18.

Before 1939 it was assumed that the epidemiology of malaria in Borneo was similar to that in Malaya, and that the disease was carried mainly by *Anopheles maculatus*. Epidemiological survey in 1939 to some extent supported this assumption, except that one village was, inexplicably, relatively free from the disease, despite the presence of abundant *A. maculatus*. An investigation, to explain this, revealed a general scarcity of *A. maculatus* in malarious villages, and later work showed that this mosquito fed predominantly on animal blood and was therefore unlikely to be a vector. Further work showed that only one species, *A. leucosphyrus*, had a preference for human blood ; it was recovered in numbers from human-bait traps, and on dissection 25 specimens were found to be positive [the number dissected, and the numbers with sporozoites and oöcysts, are not stated] ; 2,700 dissections of other species, including *A. maculatus*, were negative.

A. leucosphyrus appears to be the most widely distributed mosquito in Borneo ; it enters houses after midnight, feeds on the sleeping inhabitants and leaves before dawn, so that it is rare in daytime catches. It breeds entirely in the jungle and is easily controlled by localized jungle clearing around its breeding places, and this is probably the simplest method of preventing malaria in Borneo, in contrast to Malaya, where the land becomes malarious after the clearing of jungle and the consequent introduction of *A. maculatus*.

The author concludes that though *A. leucosphyrus* is often said to be harmless, yet wherever it has been studied in adequate numbers it has always been found positive on dissection, and that it " may prove to have much more relation to malaria in other parts of the world than has hitherto been supposed, its presence being masked by its elusiveness, and its virulence by the presence of some other much more easily captured and incriminated mosquito."

G. Macdonald.

Downs, W. G. & Pittendrigh, C. S. **Bromeliad Malaria in Trinidad, British West Indies.** *Amer. J. Trop. Med.* 1946, Jan., v. 26, No. 1, 47–66, 7 figs. [20 refs.]

This is an admirably concise and complete account of the complicated problems attendant upon the control of malaria transmitted by bromeliad-breeding anophelines of the subgenus *Kerteszia* in Trinidad. The history of investigations on bromeliad malaria is outlined. In 1935 de Verteuil [this *Bulletin*, Supplement, 1936, v. 33, 261] published a detailed malaria survey of cacao-growing areas of Trinidad, and concluded that the high malaria incidence and mortality of these areas was due to *A. bellator*. This conclusion was subsequently fully confirmed by Rozeboom and Laird [this *Bulletin*, 1942, v. 39, 664] and by Downs, Gillette and Shannon [this *Bulletin*, 1944, v. 41, 445].

Throughout a large part of the centre of Trinidad, forest has been replaced by plantations of *Theobroma cacao* (cocoa). The cacao trees are protected by tall, regularly interplanted shade trees, immortelles, *Erythrina glauca* and *E. micropteryx*. The plantations as a whole constitute an extensive artificial forest which supports a large human population. The immortelle trees are very heavily parasitized by bromeliads. Thirty-four species of bromeliads have been found on these shade trees of Trinidad cacao estates: five of these species are universal, being found on almost every tree. On 50 sample trees the average number of bromeliads per tree was 66. The number of immortelle trees to the acre varies from 11 (in abandoned areas) to 64. The different bromeliads are by no means of equal value as host plants of *A. bellator*; there is a host-plant selection on the part of this anopheline. The two commonest large bromeliads are *Aechmea nudicaulis* and *Gravisia aquilega*: they form nearly a half of the total immortelle community of bromeliads. *Gravisia aquilega* is by far the most important; it is rare to find a plant that does not contain *A. bellator* larvae. It is equally rare to find *A. bellator* larvae in *Aechmea nudicaulis*. *A. bellator* does not occur in all the parts of Trinidad where cacao estates exist, but is restricted to areas of high rainfall.

A. bellator occasionally enters dwellings to feed, but it leaves for forest cover immediately after feeding. This behaviour precludes the possibility of control by spray killing adult mosquitoes. It has a well-marked evening flight, but is active throughout the day in cacao plantations. The greater part of malaria transmission takes place either in the plantations, where labourers are freely attacked, especially on damp days, or on the verandahs of houses in the evening.

As a malaria control measure the manual removal of bromeliads has been tried, but it is excessively costly. Moreover, immortelle trees are difficult and dangerous to climb. Large thorns cause bad scratches or open lacerations; scorpions, spiders and snakes are harboured by the epiphytes; the limbs of the tree are extremely brittle; and climbing is almost impossible when the tree is wet.

Spraying with copper sulphate solution can destroy bromeliads: a heavy spraying equipment developed by the U.S. Department of Agriculture for the control of the gypsy moth has been used with success.

A change in agricultural practice, whereby shade trees are abandoned and the cacao trees protected by rows of trees planted " perpendicular to the prevailing wind," is now being encouraged by the Government of Trinidad. For such windbreaks the mango tree would be suitable. Should this change materialize, endemic bromeliad malaria should disappear from the centre of the Island. *Norman White.*

Moore, J. A., Young, M. D., Hardman, N. H. & Stubbs, T. H. **Studies on Imported Malarias : 2. Ability of California Anophelines to transmit Malarias of Foreign Origin and other Considerations.**. *J. National Malaria Soc.* Tallahassee, Fla. 1945, Dec., v. 4, No. 4, 307–29. [13 refs.]

Californian anophelines were fed on volunteer returned service men suffering from relapsing malaria acquired overseas. Four species of *Anopheles* were used : *A. maculipennis freeborni*, *A. m. occidentalis*, *A. pseudopunctipennis franciscanus* and *A. punctipennis*. *A. m. freeborni* was used as the standard testing species ; the others were compared with it. Some 100,000 anophelines were handled during the course of the work ; most were reared in an insectary. Eighty-nine " lots " of mosquitoes were fed on 73 patients, most of whom had strains of malaria parasites acquired in the South Pacific. There was one *P. falciparum* infection, the rest were *P. vivax*. Of 14,640 mosquitoes applied, 11,592 fed. After feeding, the mosquitoes were kept in a cabinet at a temperature of 75°F. and a relative humidity of 80 to 90 per cent.

Of 64 " lots " fed on 62 soldiers with relapsing Pacific *P. vivax* infections, 48 became infected. In these infected lots 2,711 *A. maculipennis freeborni* were dissected ; 1,428 were infected (52·67 per cent.). (A " lot " is 100 or more mosquitoes of the same species fed upon a patient at one time.)

Seventeen different infections were transmitted to 21 patients ; there were two failures to transmit in the case of Negroes and who had had malaria before.

A. maculipennis occidentalis, *A. punctipennis* and *A. pseudopunctipennis franciscanus* appeared to have the same susceptibility to infection as has *A. maculipennis freeborni*. The length of the sporogenous cycle at 75°F. in all four species was about 10 days. At outdoor temperature, infection developed at Marysville, California, in September–October, but much more slowly than in mosquitoes kept at 75°F. In San Francisco infections did not develop during a 19-day period at what is usually the warmest season of the year ; but the parasites were still viable, and development was completed when the mosquitoes were transferred to a temperature of 75° at the end of 19 days.

The gametocyte count in soldiers with relapsing malaria averaged 4·5 per 100 white blood cells. Infections occurred most frequently when there were between 1 and 15 gametocytes per 100 white cells, the highest infectivity, 73·8 per cent. of the mosquitoes fed, being obtained within the range of 6–10 gametocytes per 100 white cells.

Foreign strains of *P. vivax* produced infections in neurosyphilitic patients similar to infections produced by indigenous strains, as regards duration of fever peaks, parasite densities and response to thio-bismol.

Norman White.

Sharnoff, J. G., Geiger, J. & Selzer, Isidore. **Malaria transmitted by Bank Blood Transfusion.** *Amer. J. Clin. Path.* 1945, Nov., v. 15, No. 11, 494–5.

Notes are given of two cases in which malaria infection was transmitted accidentally by blood transfusion. In one case blood that had been stored eight days appeared to have been responsible for a *P. malariae* infection, though all attempts at demonstrating the parasite in the donor's blood were unsuccessful. The other was a tertian infection ; the donor had had fever in Porto Rico two years previously. The authors recommend that the blood of all persons from known malarious areas should be classed as not acceptable for transfusion, unless the blood be used for plasma. The storage of blood for eight days is not an adequate safeguard against malaria transmission.

Norman White.

Boyd, M. F. & Kitchen, S. F. **On the Heterologous Value of Acquired Immunity to *Plasmodium falciparum*.** *J. National Malaria Soc.* Tallahassee, Fla. 1945, Dec., v. 4, No. 4, 301–6.

The published data refer to 10 white and 21 coloured patients whose *P. falciparum* infections were induced by inoculations with infected blood. Four of the strains used were indigenous and four exotic, from Cuba, Mexico, Panama and Trinidad, respectively.

Original infections were markedly more severe in white than in coloured patients. Convalescents from artificially induced *P. falciparum* infections usually exhibit a clinical tolerance when reinoculated with a heterologous strain of this parasite, as manifested by a shorter period of clinical activity. Infections in white patients thus reinoculated resemble primary infections in coloured patients, both exhibiting but one wave of trophozoites, followed by a wave of gametocytes. The density of the parasitaemia caused by heterologous reinoculation may be greater than that of the original infection, but it is usually lower. Gametocyte production is often greater after heterologous reinoculation of coloured patients than it was after the primary infection. It would seem that the immunity acquired during convalescence from a *P. falciparum* infection has an appreciable heterologous value. *Norman White.*

Milovzorova, E. N. [**The Influence of Two-Years' Sojourn of Non-Immune Persons in a Malarial Locality of Middle Asia on Malaria Morbidity and Mass Relapses after their Re-Evacuation into Moscow Province.**] *Med. Parasit. & Parasitic Dis.* Moscow. 1945, v. 14, No. 5, 76–84, 1 chart. [24 refs.] [In Russian.]

In 1942, 450 persons of different ages were evacuated from Leningrad to Middle Asia. The introduction of this group of non-immune people into an endemic area of malaria resulted in an outbreak of the disease, which forms the subject of this communication. In 1942–43 the incidence of malaria (malignant and benign tertian) amounted to 36 per cent., with 40 per cent. relapses a year later (1944), owing to insufficient and unsystematic treatment, as well as on account of lowered resistance under the severe conditions imposed by the war. On the return of this group to Moscow Province, numerous relapses occurred during the first half-year of 1944.

It is pointed out that owing to the movements of the population of U.S.S.R. resulting from the war, there is a danger of introduction of malaria into non-endemic areas, necessitating the prompt adoption of anti-malaria measures among contingents arriving from endemic areas. Among these measures are noted examination of such persons, record of cases, and drug treatment of clinical cases, as well as anti-relapse treatment. *C. A. Hoare.*

Wartman, W. B. & Shlimovitz, N. **The Blood Protein Tyrosine Reaction in Malaria, Acute Epidemic Hepatitis, and certain other Diseases.** *Amer. J. Med. Sci.* 1946, July, v. 212, No. 1, 60–67, 2 charts.

" 1. Blood protein tyrosine (euglobulin) level was studied in patients with relatively acute malaria (*P. vivax*) 3 months after they had left the malarious district.

" 2. In these patients, and under the condition of the study the test was of limited diagnostic value, because 40% of those with positive blood films had a normal blood protein tyrosine. It was not of value in predicting relapses.

" 3. Elevated readings in patients with malaria returned to normal within a few months.

" 4. Blood protein tyrosine was elevated in many cases of acute epidemic hepatitis."

Most, H. & Hayman, J. M., Jr. **Uncommon Clinical Manifestations of Vivax Malaria.** *J. Amer. Med. Ass.* 1946, Feb. 23, v. 130, No. 8, 480–85.

Delayed primary attacks of malaria in the returned serviceman, some time after the cessation of effective suppressive treatment, may be bereft of the symptoms which characterize a typical attack, and it may not be possible to find parasites in blood smears for some days. Persistence and patience in the examination of blood smears may result in finding *P. vivax* and useless treatment with penicillin or sulphonamides may thus be avoided.

Symptoms and signs suggestive of an abdominal disease may precede or accompany an acute attack of *vivax* malaria ; blood smears should be examined carefully before recourse is had to surgery. The white blood cell count is rarely increased in malaria.

Convulsions may occur with attacks of *vivax* malaria, as a reaction to hyperpyrexia or in patients with underlying brain disease. Pre-existing epilepsy, head injury and *falciparum* malaria must be excluded. A stiff neck and fever may simulate meningitis.

Urticaria or severe angioneurotic oedema may precede or accompany acute attacks of *vivax* malaria.

Pulmonary signs and symptoms in attacks of *vivax* malaria may suggest a diagnosis of pneumonia in the winter months.

Surgical operations or trauma may reactivate *vivax* infections long after the last clinical manifestation of malaria.

Malaria does not exclude the possibility of other co-existing infections.

Norman White.

Downs, W. G. **Results in an Infantry Regiment of Several Plans of Treatment for Vivax Malaria.** *Amer. J. Trop. Med.* 1946, Jan., v. 26, No. 1, 67–86, 4 figs.

This report deals with the experience of two battalions of an infantry regiment which were for periods of 189 and 164 days, in 1942–43, on Guadalcanal, a highly malarious island, and thence were transferred to Samoa, which is malaria-free, for " demalarialization ". While in Guadalcanal, first quinine and then mepacrine suppressive therapy was administered, but was not rigidly enforced except in the last two months of the regiment's service on that island. Forty-eight per cent. of the regiment suffered from malaria in Guadalcanal, and the monthly malaria incidence rates varied from 800 to 1,500 per 1,000 per annum : most of the diagnoses were clinical.

For " demalarialization " in Samoa, where there were laboratory facilities, different groups of men were subjected to different treatments. The results are recorded in detail. The conclusions are summarized as follows :—

" In troops almost universally infected with vivax malaria, few or no individuals were cured of infection by suppressive atabrine therapy (0·4 gm. per week) administered for a period of six months during exposure on a malarious island.

" Few or no cases of vivax malaria were cured by mass therapy with atabrine or with atabrine plus plasmochin after leaving the malarious island.

" Initial attacks of malaria occurred as late as six months or more after discontinuing atabrine suppression or after mass therapy of any of the types employed.

" Atabrine mass therapy did not alter appreciably the number of first relapses occurring after first observed attacks.

" There was a definite tendency to relapse between the fifth and seventh week after the first observed attack, with a sharp peak in the sixth week.

" No difference in course of disease was noted between the group which had had malaria attacks previously on the malarious island and had first observed attacks during the course of this study and the group which had not had malaria attacks on the malarious island and had actual primary attacks during the course of study. (The total time span from date of first exposure to infection to termination of study was one year.)

" Plasmochin administered as a part of mass therapy apparently aided in lowering the peak rate of first observed attacks, and spread the experience over a longer time period without appreciably altering the final outcome as far as first observed attacks and first relapses are concerned. There may have been a slight tendency to lower the ratio of total relapses to first observed attacks, but this point is far from being clearly established and needs observation over a longer period of time." *Norman White.*

KNOX, W. E. **The Quinine-Oxidizing Enzyme and Liver Aldehyde Oxidase.** *J. Biol. Chem.* 1946, June, v. 163, No. 3, 699–711, 4 figs. [16 refs.]

A derivative of quinine was obtained by KELSEY *et al.* [this *Bulletin*, 1944, v. 41, 923] when minced rabbit liver was incubated with the alkaloid. It was shown by MEAD and KOEPFLI [this *Bulletin*, 1945, v. 42, 9] to be an oxidation product of the parent substance in which the hydrogen atom in the position adjacent to the nitrogen atom of the quinoline nucleus had been replaced by a hydroxyl group. The enzyme involved has now been prepared in approximately 5 per cent. purity and its activity determined under standard conditions by the rate of reduction of methylene blue in the presence of cinchonidine as substrate. Rabbit liver was found to be the only satisfactory source of the enzyme which has been shown to oxidize quinoline, isoquinoline and pyridine rings in the corresponding position to that found for quinine. The rate of oxidation was dependent on the reactivity of the hydrogen atom in that position. It is possible that the slower oxidation of certain substituted quinolines by enzyme action may help to explain their antimalarial activity. Plasmoquine and substances with other heterocyclic or aromatic rings were not oxidized by this enzyme, which has properties similar to those of liver aldehyde oxidase. It is soluble in water, resistant to a temperature of 60°C. for five minutes and is precipitated at 25–40 per cent. saturation with ammonium sulphate; in properties it resembles a similar preparation from pig liver. Whereas that from rabbit liver could oxidize quinolines as well as aldehydes, the other preparation reacted with aldehydes only. The enzymes from the respective sources are both flavo-proteins. No separation of the substances involved in the oxidation of quinolines or aldehydes could be achieved, and in the presence of both types of substrate the rate of reaction was slower than with either type alone. The mutual interference by the two substrates suggests that both reactions share a common element in the pathway of oxidation which available evidence suggests to be the flavin group. *J. D. Fulton.*

MOST, H. & HAYMAN, J. M., Jr. **Relative Efficiency of Quinacrine (Atabrine) and Quinine in Treatment of Acute Attacks of Vivax Malaria.** *Amer. J. Med. Sci.* 1946, Mar., v. 211, No. 3, 320–24, 2 charts.

Three hundred and ninety-seven patients with acute attacks of *P. vivax* malaria, with fever and parasitaemia, were treated with mepacrine (quinacrine). All treatment was begun on the day following the onset of the attack. On the first day of treatment 1 gm. of mepacrine was given by mouth, in three divided

doses. On the succeeding six days 0·1 gm. was given three times a day after meals. The total dose given over the seven-day period was thus 2·8 gm. Parasite counts were done twice daily and continued till negative for three consecutive days. Plasma-mepacrine levels were determined on the 2nd and 8th days. The patients left the ward on the 8th day and 200 of them were observed for 120 days, or till relapse. During this time smears were examined twice weekly. A rise of mouth temperature over 100°F., associated with parasitaemia, was considered a relapse, and the patient was re-admitted to hospital.

One hundred similar patients were treated with quinine, the treatment starting the day after the onset of the attack. On the first day 1 gm. was given thrice, at intervals of 8 hours. On each of the following 13 days, 2 gm. were given in three divided doses. Thus 29 gm. of quinine sulphate were given by mouth during the 14 days. Minimum and maximum plasma-quinine determinations were made on the 2nd, 7th and 14th days of treatment. The other observations were the same as described for the mepacrine group.

Mepacrine cleared the peripheral blood of parasites more rapidly than did quinine. At 48 hours from the commencement of treatment, 77 per cent. of the mepacrine patients were free from parasites, as compared with 44 per cent. of the quinine patients.

Of the patients treated with mepacrine, 7 per cent. had fever of 100·2 or higher on the 2nd or 3rd day of treatment, as compared with 10 per cent. of those treated with quinine. In the treatment of delayed primary attacks of *vivax* malaria, 32 per cent. of patients treated with quinine had fever on the 2nd or 3rd days, as compared with 16 per cent. of similar patients treated with mepacrine.

All concerned with these observations were agreed that mepacrine is more effective than quinine in the prompt control of symptoms of an acute attack of malaria.

With regard to toxicity, the only points in favour of either drug are the absence of tinnitus with mepacrine. Rare cases of idiosyncrasy or sensitization to either drug may occur. Patients with eczematoid or exfoliative dermatitis and acute malaria should not be given mepacrine if they have had the drug before.

Eighty per cent. of Pacific infections relapsed within the 120 days of observation, regardless of the drug used in treatment. The mean interval to relapse after mepacrine was 53 days, and after quinine, 22 days.

The observations show that mepacrine is superior to quinine in the treatment of acute attacks of *vivax* malaria. *Norman White.*

TOOMEY, A. G. **Aspects of the Treatment of Subtertian Malaria.** *J. Roy. Nav. Med. Serv.* 1946, Jan., v. 32, No. 1, 32–8, 1 fig.

This paper is based on the treatment of 883 adult European patients suffering from *P. falciparum* malaria in Freetown, Sierra Leone, during 1943–44. Various forms of treatment are compared. Mepacrine was preferred to quinine ; relapses were fewer after its use. The average amount of mepacrine given in a twelve-day course was 5·4 gm. ; 1·2 gm. the first day ; 0·9 gm. the second day ; 0·6 gm. the third day ; and 0·3 gm. daily thereafter till the end of the course. In 157 cases, the dose of mepacrine was doubled on each of the last four days of the course, during which the patient was given graduated walking and running exercise. When necessary, mepacrine was given by both intramuscular and intravenous routes, without any ill effect ; it was preferred to quinine similarly administered. After the introduction of mepacrine as a suppressive, pamaquin was badly tolerated and its use in treatment was discontinued. [Pamaquin is

said to have been given in doses of 0·1 gm. thrice daily for four days, probably a misprint for 0·01 gm.] *Norman White.*

Gordon, H. H., Marble, A., Engstrom, W. W., Brunsting, H. A. & Lippincott, S. W. **Relapses following Delayed Treatment of naturally induced *Vivax* Malaria of Pacific Origin.** *Science.* 1946, Mar. 29, 391–2. [10 refs.]

Sixty-nine white soldiers, who required malaria therapy for neurosyphilis, were infected with U.S. anophelines which had previously been fed on soldiers infected with *P. vivax* malaria acquired in the Pacific area. Antimalarial treatment (2·8 gm. mepacrine in 6 days) was delayed in the patients suffering from neurosyphilis until they had had from 8 to 15 paroxysms with an average of 40 hours of fever over 104°F. This level was reached on the average in 20 days during which blood smears revealed *P. vivax*. The patients were then observed till a relapse occurred or for at least 60 days without a relapse : thick blood smears were examined twice weekly.

Forty-five patients (65 per cent.) had a relapse. There was no significant difference between the mean hours of fever above 104°, or between the mean days of parasitaemia, in those patients who relapsed and those who did not. The relapse rate was not markedly different in another group of 124 patients suffering from Pacific *P. vivax* malaria, whose attacks were promptly treated with mepacrine in the Harmon General Hospital.

Seventy-six per cent. of the relapses following delayed treatment occurred within 59 days, and 93 per cent. within 89 days of the termination of treatment.

Relapses occurred in men infected with 7 of the 10 strains of *P. vivax* used. Only 7 men had been infected with the 3 strains that caused no relapse. The importance of the strain in determining relapse rates is illustrated by the fact that only 2 of 16 soldiers infected with *P. vivax* of the Mediterranean origin relapsed, and these after intervals of 111 and 189 days from the termination of mepacrine treatment. No relapse followed the primary manifestations of infection induced in 28 men by the intravenous inoculation of trophozoites of Pacific strains which had caused very high relapse rates when infection had been conveyed by mosquito bite. No evidence was forthcoming that early treatment of malaria attacks delays the development of immunity.

Norman White.

Ginsberg, J. E. & Shallenberger, P. L. **Wood's Light Fluorescence Phenomenon in Quinacrine Medication.** *J. Amer. Med. Ass.* 1946, July 6, v. 131, No. 10, 808–9.

Ginsberg accidentally observed that his finger nails emitted a bright greenish-yellow fluorescence when he was examining a child for tinea capitis under Wood's light ; he had recently returned from the tropics, and presumably his skin and its appendages were still stained with mepacrine. Shallenberger had made a similar observation whilst making an earlier study concerning deposits of the drug in the hard palate and finger nails (*Arch. Dermat. & Syph.* 1946, v. 53, 349).

These authors collaborated in a study of 511 patients, 158 of whom had taken mepacrine ; in 79 of the latter the greenish-yellow fluorescence did not occur, but 55 had not taken the drug for 13 months. On investigation it was found that the characteristic fluorescence occurred in all subjects who were on mepacrine therapy or " sound prophylaxis " ; the fluorescence could be noted for three to six months after the drug was discontinued, but as the nails grew the proximal areas showed the normal fluorescence of healthy nails (violet-blue in colour) whilst the distal parts showed the greenish-yellow hue referred to above.

The toe-nails cleared more slowly than the finger-nails; frequently the nails of the big toes remained fluorescent longer than the others, sometimes for as long as a year after mepacrine therapy or prophylaxis ceased.

Unusual fluorescence phenomena did not occur in patients receiving numerous other drugs, including penicillin and sulphonamides.

Mepacrine tablets and aqueous solutions have a brilliant yellow fluorescence under Wood's light.

The authors suggest that there is a longer delay in the complete excretion of mepacrine from the body than has previously been reported, and consider that their observation confirms that made by LUTTERLOH and SHALLENBERGER (references quoted above) concerning mepacrine deposits, which may be seen as bluish pigmentation under the nails when examined in daylight.

[Wood's light—so called—is an ultra-violet ray filtered through glass containing nickel oxide (Wood's glass) which restricts the passage of all but relatively long wave ultra-violet light of about 3,650 Å; the " light " is commonly used for the rapid diagnosis of tinea capitis, since hairs infected with *Microspora* emit a characteristic green fluorescence.] *R. M. B. MacKenna.*

KIERLAND, R. R., SHEARD, C., MASON, H. L. & LOBITZ, W. C. **Fluorescence of Nails from Quinacrine Hydrochloride.** *J. Amer. Med. Ass.* 1946, July 6, v. 131, No. 10, 809–10, 1 fig.

Kierland, who had just returned from the south-west Pacific area where he had been taking mepacrine daily for almost two years, noted a brilliant yellow-green fluorescence of his finger nails under Wood's light. He and his colleagues have noted this phenomen in nine other persons, all of whom had taken mepacrine for from 5 to 21 months. They noted that the fluorescence begins to fade three months after the drug is discontinued, and that it usually disappears in six or seven months. In their opinion, the blue-black pigmented areas of the nailbeds and hard palate, which have been noted in persons taking mepacrine for long periods, do not fluoresce, neither does the skin or hair of these subjects; further, their teeth do not show an abnormal fluorescence.

The exciting wavelength of the Wood's light used in this study was 3,500–4,000 Å; the wavelength of the light emitted by the fluorescing nails was 5,400–6,000 Å. The fluorescent wavelength of solutions extracted from the skin, nails and hair of a person receiving mepacrine was 5,300–5,800 Å. Quantitative photofluorometric determinations were made of the skin and its appendages in three persons. The results are tabulated thus :—

Mepacrine in Micrograms per Gram of Tissue.

Nails	Hair	Skin
1. 2·6	1. 27·2	1. 10·4 wet weight
2. 5·2	2. 47·6	28·1 dry weight
3. 0·63*		

* This person had discontinued taking mepacrine three and a half months before the clippings of nail were obtained.

The authors suggest that it would be interesting and valuable to determine the amounts of mepacrine in the affected and non-affected areas of skin of persons with the " atypical lichen planus " syndrome.

R. M. B. MacKenna.

LIPPINCOTT, S. W., ELLERBROOK, L. D., HESSELBROCK, W. B., CARRICO, C. C. & MARBLE, A. **The Relationship of Spinal Fluid to Plasma Concentrations of Quinacrine and Quinine.** *J. National Malaria Soc.* Tallahassee, Fla. 1946, Mar., v. 5, No. 1, 85–91.

The concentration of quinacrine (atebrin, mepacrine) and quinine has been simultaneously determined in the plasma and spinal fluid of two groups of neurosyphilitic patients, as a guide to the mode of action and effectiveness of these drugs in cerebral malaria. In one experiment, 51 patients, divided into 7 groups, were given quinacrine in the form of atebrin dihydrochloride in doses ranging from 0·5 to 3·0 gm. over a period of 1–3 days, so that the plasma concentrations equalled, or were greater than, those obtained during therapy. These concentrations were maintained for different periods, the range encountered being from 18 to 135 micrograms per litre for plasma and from 0 to 6 micrograms per litre in the case of spinal fluid, the values for a large percentage of the latter being within the range of error of the method. Specimens of plasma and spinal fluid were obtained from 2 to 61 hours after the last dose of drug, the latter being withdrawn immediately prior to the venous blood specimen. The method of BRODIE and UDENFRIEND [this *Bulletin*, 1944, v. 41, 453] was used for the estimation of atebrin after trial and with slight modifications for quinine. In spinal fluid, the concentration of quinacrine varied from 0 to 15 per cent. of that in plasma, and the ratio was not appreciably affected, in the different groups, by variation in conditions of dosage and withdrawal. In similar experiments, quinine sulphate dihydrate was given to 44 subjects in doses ranging from 0·5 to 3·0 gm. during twenty-four hours. Specimens were obtained from 2·0 to 3·5 hours after the last dose. The plasma levels at their peak values varied from approximately 1,000 to 7,000 micrograms per litre in six different groups on different dosage schedules. The corresponding variations in spinal fluid level were from 19 to 260 micrograms per litre. The maximal ratio of the latter to that in plasma in one case reached 9 per cent., but was generally much lower. It appears that the ratio increased in proportion as the plasma concentration was increased, and as the time of maintenance of the latter lengthened. The authors believe that the mechanism of exchange of quinacrine between plasma and spinal fluid is one of diffusion. Both drugs are probably bound to protein in plasma, and hence the smallness of the spinal-fluid/plasma ratio. It is doubtful if the concentrations of quinacrine and quinine in the spinal fluid obtained with the non-toxic doses used could be of therapeutic value in cerebral malaria if these drugs were in combination with protein. *J. D. Fulton.*

WILLIAMSON, Anne, HEGSTED, D. M., MCKIBBIN, J. M. & STARE, F. J. **The Effect of Variations in the Level of Dietary Calcium upon the Growth of Young Rats receiving Atabrine.** *J. Nutrition.* 1946, June 10, v. 31, No. 6, 647–55.

When recently weaned male rats were given a standard diet, to 100 gm. of which 40 to 60 mgm. of mepacrine was added, the rate of growth was significantly lowered as compared with that of controls given no mepacrine. This inhibition of growth was more marked when the diet contained 1·35 per cent. of calcium than when it contained either 0·55 or 0·15 per cent. The concentration of mepacrine in the liver was much greater in animals given the high calcium diet than in those given the low calcium diet, although the intake of mepacrine was approximately the same in the two groups. The concentration of mepacrine in the liver was the same after 30 days and after 63 days of treatment.

The reaction of the contents of the distal small intestine and caecum was more alkaline in the animals taking the high calcium diet. The addition of various

salts to the diet failed to show any effect of alteration of intestinal *p*H upon the toxicity of mepacrine. Some animals on the high calcium diet exhibited renal calculi which may have impaired the excretion of mepacrine. It is therefore not clear whether the increased toxicity of mepacrine when combined with a high calcium diet is due to increased absorption, decreased excretion, or to a specific effect of calcium on mepacrine metabolism. *H. E. Harding.*

Imperial Chemical (Pharmaceuticals) Limited. Biological Department. **Paludrine—a Summary of Information to February, 1946** [Davey, D. G.]. 1946, Mar. 1, 13 mimeographed pp. [19 refs.] [Report No. B.T. 1166.]

This is a most useful summary of information about Paludrine. Work on this drug is still being continued because there are points on which insufficient information exists, but this account, by bringing together all the available results of investigation, presents a picture which will be of very great value to those who work on the chemotherapy of malaria and, no less, to those who must plan ahead for treatment policies.

To attempt an abstract of this already condensed summary would scarcely be possible; it is enough to indicate briefly some of the conclusions which existing work permits. The author assumes, by analogy, that exo-erythrocytic forms of the human malaria parasites exist, though he admits that they have not yet been found.

Two salts of Paludrine have been used, the monohydrochloride and the monoacetate; each is sparingly soluble in water. The fatal dose for acute poisoning in animals is from 25 to 80 mgm. per kgm., for chronic poisoning from 20 to 60. Paludrine is rapidly absorbed and excreted, chiefly in the urine; though the blood concentration is much diminished 12 hours after administration, a build-up may be effected if doses are taken twice each day.

In man, one to three daily doses of 100 mgm. or less [these are total doses, not doses per kgm.] may completely and permanently prevent *P. falciparum* from gaining access to the blood stream, even if taken on the day after exposure to infected mosquitoes. There is evidence of an inhibitory action on the presumed exo-erythrocytic forms of *P. vivax*, but the fact that relapses do occur after cessation of this treatment shows that the action is not lethal.

The suppressive effect of Paludrine is almost perfect; a daily dose of 25 mgm. is enough completely to suppress subtertian, and of 100 mgm. to suppress benign tertian, malaria. Moreover, since a single dose of 100 mgm. is enough to control a clinical attack so that relapse does not occur for several weeks, the same dose, given once each week, is likely to be an efficient suppressive dose.

In man, slight toxic symptons may be produced with 500 mgm. twice daily for 28 days; single doses of more than 750 mgm. should not be given. In treatment it is wise to distinguish between clinical cure and radical cure; in subtertian malaria the former can be achieved by a single dose of 100 mgm., or by repeated doses of 50 mgm.; the latter by 100 mgm. t.d.s. for 10 days. In benign tertian malaria clinical cure can be achieved by similar doses, but radical cure cannot be guaranteed; relapses do occur, though with bigger doses, up to 500 mgm. twice daily for 14 days, patients are apparently slow to relapse. After treatment, patients may be released with a supply of Paludrine, to be taken as a weekly dose of 100 mgm. for several months. In quartan malaria Paludrine apparently has good effect, but there have been too few cases to make general claims. Intravenous injections have been used, and in subtertian malaria a dose of only 5 mgm. given by this route has marked effect.

Paludrine does not destroy gametocytes, but renders them non-effective for mosquitoes for several days; this seems to be due to the action of the drug while in the stomach of the mosquito.

The author quotes much already published work, most of which has already been abstracted in this *Bulletin*. *Charles Wilcocks.*

Most, H., London, I. M., Kane, C. A., Lavietes, P. H., Schroeder, E. F. & Hayman, J. M., Jr. **Chloroquine for Treatment of Acute Attacks of Vivax Malaria.** *J. Amer Med. Ass.* 1946, July 20, v. 131, No. 12, 963–7, 5 charts.

A report on the activity of the antimalarial drug chloroquine (SN 7618) : 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, which was recently synthesized in America, has been reviewed [this *Bulletin*, 1946, v. 43, 708]. In the present study its value in the treatment of acute attacks of malaria due to infection with *P. vivax* acquired in the Pacific and Mediterranean theatres of war, has been investigated in primary and relapse cases. More than 500 patients were treated whom it was possible to follow up until relapse occurred, or for a period of 120 days after the end of treatment. The cases were grouped according to origin and stage of infection. Several dosage schedules were employed in which 0·8–2·0 gm. of the drug was administered, and 50–75 cases were treated in each group. The schedules in which 1·0 gm. was given on one day, 1·5 gm. in 4 days or 2·0 gm. in 7 days proved satisfactory. Comparison was also made of the results obtained in patients treated with 2·8 gm. quinacrine (atebrin) during a period of 7 days, or with 29·0 gm. quinine during 14 days. It was found that chloroquine freed the peripheral blood from parasites, abolished fever and controlled other symptoms more rapidly than the other two drugs. No major toxic manifestations were caused by chloroquine, but about 20 per cent. of the patients had general or localized pruritus of a slight or transient character. In 2 per cent. pruritus was accompanied by skin eruptions. Relapse rates 120 days after treatment were slightly lower than with quinine or atebrin, but these relapses with the new drug occurred much later in the observation period. Malaria acquired in the Pacific was more prone to cause relapses than that acquired in the Mediterranean area, and no radical cures were obtained with any of the drugs. Plasma levels of chloroquine are recorded for 176 patients treated as above, and it was found that a minimum concentration of approximately 10 micrograms per litre was necessary to control an acute attack. [After therapeutic doses of Paludrine, 10–100 micrograms of the drug are present per litre of plasma.] The authors summarize the reasons for their conclusions that chloroquine is a safe and highly effective drug, which is superior to quinine and quinacrine under the above conditions of test. A course of treatment for acute attacks of malaria due to *P. vivax* is outlined.

J. D. Fulton.

Barber. H. J. & Wragg, W. R. **Contributions to the Chemistry of Synthetic Antimalarials. Part II. Tetrahydropamaquin.** *J. Chem. Soc.* 1946, July, 610–13.

Barber, H. J., Major, F. W. & Wragg, W. R. **Contributions to the Chemistry of Synthetic Antimalarials. Part III. An Open Ring Analogue of Tetrahydropamaquin.** *J. Chem. Soc.* 1946, July, 613–16.

Madinaveitia, J. **The Antagonism of some Antimalarial Drugs by Riboflavin.** *Biochem. J.* 1946, v. 40, No. 3, 373–5, 1 fig.

In an investigation relating to the mode of action of antimalarial drugs, the antagonism by these and other compounds of riboflavin, an essential metabolite

for *Lactobacillus casei*, has been studied. For this metabolite, which the organism cannot synthesize and which plays a part in enzyme systems, an extraneous supply is necessary. The present indirect approach to the problem was made because of the lack of knowledge of the essential requirements of malaria parasites. The explanation of the action of a drug in some cases appears to depend on the fact that it bears a similarity in molecular shape to the metabolite. Such similarity in structure between riboflavin and certain antimalarials has been indicated by CURD *et al.* [this *Bulletin* 1946, v. 43, 394]. A suitable medium for the lactobacillus is described, in which growth was measured turbidimetrically. To observe the effect of riboflavin on the inhibition of growth by drugs, the former was made up in various concentrations in the medium, which was then sterilized and inoculated with the test organism in bulk. To series of tubes containing the drugs for assay in various dilutions was added the medium with the organism and the different concentrations of riboflavin. After incubation, the presence or absence of growth was determined. Of the various substances tested, it was found that only those having antimalarial properties were antagonized by riboflavin, the effect being most marked at relatively high concentrations of the latter. *J. D. Fulton.*

i. TONKIN, Isabel M. & WORK, T. S. **A New Antimalarial Drug.** [Correspondence.] *Nature.* 1945, Nov. 24, 630.

ii. MUKERJI, B. **Antimalarial Drugs of the Indigenous Materia Medica of China and India.** [Correspondence.] *Ibid.* 1946, Aug. 3, 170.

i. The authors have made animal experiments with samples of two Chinese plants, reputed to possess antimalarial properties. These were *Fraxinus malacophylla* and a root known as '*chang shan*' which is reputed to be *Dichroa febrifuga*.

The first plant was found to be without action on *Plasmodium gallinaceum* in chicks. Extracts of the second plant showed considerable activity against a trophozoite—induced infection of *P. gallinaceum* in chicks. No alkaloid could be found in either plant.

ii. Mukerji also tested *F. malacophylla* on simian and human malaria. His observations confirmed those of TONKIN and WORK (see above) in the case of chicks [although, in fact, he claims that these authors' observations differed from his, since they recorded "considerable activity against *P. gallinaceum* in chicks." In fact, this statement, as will be seen above, referred, not to the use of *F. malacophylla* but to *D. febrifuga* (*chang shan.*)].

In benign and malignant human malaria, Mukerji could find no proved antimalarial effect on the part of *F. malacophylla*, using it in three forms; but in two of four cases, a temporary febrifugal effect with a brief disappearance of the malaria parasites, was recorded; both cases relapsed.

The same phenomenon was observed with two indigenous Indian drugs, *Alstonia scholaris* and *Caesalpinia bonducella*. The author also examined Indian counterparts of *F. malacophylla* without success.

He concludes that in India and China, certain indigenous vegetable drugs have earned a reputation as malaria cures on the strength of slight febrifugal properties with temporary disappearance of malaria parasites; but that they have no true anti-plasmodial effect.

H. J. O'D. Burke-Gaffney.

i. Heidelberger, M., Coates, W. A. & Mayer, M. M. **Studies in Human Malaria. II. Attempts to influence Relapsing Vivax Malaria by Treatment of Patients with Vaccine** (*Pl. vivax*). *J. Immunology.* 1946, May, v. 53, No. 1, 101–7.

ii. ——, Prout, C., Hindle, J. A. & Rose, A. S. **Studies in Human Malaria. III. An Attempt at Vaccination of Paretics against Blood-borne Infection with** *Pl. vivax*. *Ibid.* 109–12.

iii. ——, Mayer, M., Alving, A. S., Craige, B., Jr., Jones, R., Jr., Pullman, T. N. & Whorton, M. **Studies in Human Malaria. IV. An Attempt at Vaccination of Volunteers against Mosquito-borne Infection with** *Pl. vivax*. *Ibid.* 113–18. 1 fig.

i. The authors have attempted to influence the relapse rate in chronic cases of benign tertian malaria by the use of a vaccine prepared from infected blood, as described in Part I of this series [this *Bulletin*, 1946, v. 43, 816]. Three groups of approximately 60 men who had contracted *vivax* malaria in the S.W. Pacific were used. One group which served as control received only routine treatment with drugs. A second group received drug treatment for the primary attack only and was then vaccinated as described below. The third group was treated like the second, the vaccine in this case consisting of red cell stromata obtained from normal blood by treatment similar to that used in preparing the vaccine from parasitized blood. Some members of the groups had at various times previous to the start of experiment received atebrin in suppressive doses. Each group was sub-divided into two, according to blood groups, as previous experiments of other authors had shown that high α-agglutinin titres may be immunologically significant in malaria. In the present experiments, however, no increase of α-agglutinin was noted in subjects of blood group O after injection of normal or infected blood from group A subjects. The average period of observation of these cases was 7–8 months. The amount of vaccine for each person corresponded to 2–6 billion parasites or an equivalent amount of normal red cell substance. It was given in divided doses by the intracutaneous (10 per cent.), subcutaneous (40 per cent.) and intravenous routes (50 per cent.) over a period of 4–5 days. In a few cases, 2 or 3 courses of vaccine treatment were given, only Rh-negative vaccines and stromata being used on Rh-negative individuals. There were only minor untoward reactions as the result of treatment. It was found that immunization with vaccine or stromata had no effect on the relapse rate.

ii. Previous attempts at active immunization in human malaria, with inconclusive results, were reported by Konstansoff [this *Bulletin*, 1930, v. 27, 663] and by Schilling [*ibid.*, 1940, v. 37, 366]. The present authors have made the first controlled vaccination experiments against a primary attack of benign tertian malaria. Vaccines were prepared as already described with the McCoy strain of *P. vivax*. Three neurosyphilitic white males without previous history of malaria were used in the tests. The vaccine, containing a total of approximately 4 billion formolized parasites, was administered by the same three routes as in Part II above, in two courses lasting 3–5 days with a week's interval between each course. The patients were injected with ½–5 million parasites of the same strain 19–22 days after the last dose of vaccine. The subsequent results of inoculation were the same in those vaccinated as in controls. Two of the vaccinated were given quinine when the malarial attack developed and further tested for immunity by reinoculation with infected blood 13–16 days later. It was concluded that no protection had been afforded by vaccination.

iii. In this series of experiments, protection was attempted against the bites of mosquitoes infected with *P. vivax*, Chesson strain, by vaccines prepared

from the parasites of the same strain. It was not found so easy to prepare highly purified vaccines from this strain on account of the asynchronous character of the infection. Three healthy white males were vaccinated by the three routes used above, in two courses extending over a period of 13–14 days, with a three-day rest interval between the two courses. A total of approximately 10 billion parasites was given in each case. No serious toxic symptoms resulted from the vaccine, but intracutaneous administration caused severe induration and erythema at the site, while mild pain and swelling followed subcutaneous injection, and chills and fever occured after intravenous injection. The plasma of one patient showed complement fixation 10 or 20 days after vaccination, but the difficulties of preparing a suitable antigen are recognized. Three weeks after vaccination each patient was bitten by 10 mosquitoes infected with the Chesson strain of *P. vivax*, along with suitable controls. Vaccination under the conditions employed failed to influence susceptibility to malarial infection.

J. D. Fulton.

Ribbands, C. R. **The Use of DDT as a Mosquito Larvicide on Flowing Water.** *Bull. Entom. Res.* 1946, May, v. 37, Pt. 1, 105–12.

This paper records the result of applying DDT solutions in oil to running water in discrete applications, instead of as a continuous spray, amplifying the work already done by the same author on still water [see this *Bulletin*, 1946, v. 43, 409].

In streams about 2 feet broad, flowing at 12 to 15 feet per minute, 10 cc. of 5 per cent. DDT in waste engine oil eliminated 97 per cent. of anopheline larvae through a distance of 100 yards. This dose was relatively ineffective (29 per cent. kill) in a stream flowing at 35–50 feet per minute, but a 20 cc. dose gave a 99 per cent. kill over 300 yards in this faster water.

Similar experiments on a river 30 feet broad, with an average rate of surface flow of 75 feet per minute, showed that a single application of two gallons of 5 per cent. DDT gave effective control for a distance of 2,280 yards. Single applications of two quarts were relatively ineffective. As in the experiments on streams, it was noted that the maximum larvicidal effect was not produced at the site of application, but some distance downstream, as far down as 965 yards from the point of treatment ; the residual effect was most marked in the most remote stretches, probably because of the slow travel of some of the DDT. This residual effect may be due to ovicidal action of DDT, DDT clinging to eggs and killing emerging larvae, or to the maintenance *in situ* of sufficient DDT to exert a slow larvicidal effect, insufficient to kill larvae until they have progressed to the second or later instars. Though of scientific interest the effect is too unreliable to be of practical value, and should be disregarded in mosquito control.

G. Macdonald.

Cottam, C. & Higgins, E. **DDT and its Effect on Fish and Wildlife.** *J. Econom. Entom.* 1946, Feb., v. 39, No. 1, 44–52.

In a series of field trials, in which DDT solution or emulsion was sprayed from aircraft, the authors recorded effect on wildlife which may be summarized as follows :—

Arthropods.—Statistical data are not included. Records are given of the destruction of gypsy moth larvae, larvae of the spruce budworm, hemlock loopers, and Japanese beetle. The only reference to bees shows that the population of a hive exposed to a spray of 5 lb. of DDT per acre survived.

Mammals.—No decrease in the numbers of short-tailed shrew and deermouse was observed in areas treated with 2 lb. of DDT per acre.

Birds.—(*a*) 0·2 and 0·5 lb. of DDT per acre were used ; no direct effect was noted, but insectivorous birds left the treated area ; (*b*) With 1 lb. per acre, four sick birds were seen ; (*c*) With 2 lb. per acre, there was no significant change in numbers ; (*d*) With 5 lb. per acre, the population of living birds was much reduced, from 1·6 to 0·5 per acre, and dead and sick birds, and abandoned nests were observed ; (*e*) with 25 lb. per acre applied as a dust, many sick birds and abandoned nests on treated ground and land adjacent to it were noted.

Amphibians.—Frogs and tadpoles in shallow water (5 inches deep), but not in deep water, were killed by 1 lb. per acre ; 5 lb. per acre killed both in deep water as well as in shallow.

Crustaceans.—0·5 and 1 lb. per acre killed most crayfish. Blue crabs left a water area treated with 0·5 lb. per acre, and subsequently returned to it, after which they suffered a high mortality.

Fishes.—The mortality varied in different species, for details of which the original paper should be consulted. In general terms the results were :—(*a*) in ponds, doses of 0·1 lb. per acre caused a mortality, on one occasion, as high as 43 per cent. ; and 1·0 lb. per acre caused mortalities varying from 78 to 93 per cent. ; (*b*) in rivers, a dose of 0·25 lb. per acre killed " less than half " of the population of the warmer water fishes, and 1·3 per cent. of brook and brown trout ; (*c*) in lakes and wide expanses of open water, 0·4 lb. per acre killed a large proportion of the fish, about 100 dead and dying shiners and sunfish being found ; toothed herring and several species of shiners and dace were killed by 0·5 lb. per acre, and about 100,000 small dead fish were observed on one occasion along the shore of a lake treated with 0·5 lb. per acre.

In laboratory trials it was observed that field mice showed symptoms when 0·2 per cent. DDT was mixed with their food, and died when 0·4 per cent. DDT was fed to them, but showed no ill-effects when 0·1 per cent. or less was mixed with their food. Cotton-tail rabbits reacted in a similar manner. Birds fed on food adulterated with DDT in a strength of 0·05 per cent. all died, the mortality being 50 per cent. with a 0·025 per cent. mixture. Fish (bluegill and largemouth bass) were all killed when the water in which they were living was treated with 1 lb. DDT per acre, applied as an emulsion ; 50 to 60 per cent. were killed when the same quantity was applied in solution, and very few were killed when it was applied as a suspension.

The authors end with a series of recommendations for the use of DDT, of which the sixth is " *Avoid spraying water.* Because of the sensitivity of fishes and crabs to DDT do not apply direct to streams, lakes and coastal bays." [Acceptance of this recommendation would greatly limit the utility of DDT in mosquito control, and in many of the places treated, aquatic life is negligible or unimportant, but it should be borne in mind whenever the treatment of large water areas is contemplated and wherever aquatic life is utilized.]

G. Macdonald.

HEMMINGS, R. J. **An Improvised Spray Rig for the Dispersal of DDT Solutions by Airplane.** *U.S. Nav. Med. Bull.* 1946, Aug., v. 46, No. 8, 1296–301, 3 figs.

LIVADAS, G. A. **A Brief Review of Malaria Problem and Malaria Control Activities in Modern Greece.** *Academic Med.* Athens. 1946, Jan.–Feb., v. 10, Nos. 91/92. [In Greek 1–8. English summary 44–50.]

GAVIN, L. D. M. **An Outline of the Anti-Malaria Campaign of the British Land Forces in Greece during 1945.** *Academic Med.* Athens. 1946, Jan.–Feb., v. 10, Nos. 91/92. [In Greek 8–17. English summary 50–59.]

WRIGHT, D. E. **Brief Outline of Malaria Program in Greece.** *Academic Med.* Athens. 1946, Jan.–Feb., v. 10, Nos. 91/92. [In Greek 18, 1 fig. English summary 59–62, 2 figs.]

RAFFAELE, G. **Modern Views on the Biology of the Malaria Parasites.** *Acta Tropica.* Basle. 1946, v. 3, No. 1, 29-40. [33 refs.]

In this interesting article, which is well worth careful study, the author, who has made important contributions to the subject, traces the progress in our knowledge of the exoerythrocytic stages of development of malarial parasites, commencing with his demonstration of such stages in *Plasmodium relictum* after his own and HUFF's discovery of the similar stages in *P. elongatum* which, however, in many respects is an anomalous form of malarial parasite. The failure of quinine to prevent malarial infections in human beings subjected to the bites of infected mosquitoes had led JAMES to postulate a special stage which developed directly from the sporozoite. Studies on species of *Haemoproteus*, which is known to reproduce only in endothelial cells, showed that it was exceedingly difficult to demonstrate the presence of schizonts in the tissues unless these were examined soon after the infection with sporozoites had taken place. That such schizonts are present in the organs at other times is proved by BRUMPT's observation of the reappearance of gametocytes in the blood after the blood has been cleared of these forms by the administration of plasmoquine. Further evidence of the development of exoerythrocytic stages from sporozoites is afforded by the lack of infectivity of the blood after injection of sporozoites. Blood taken from birds or human beings during the first four to six days after sporozoite infection fails to produce infection when injected even in relatively large amounts into uninfected birds or human beings. Such a negative phase does not occur when infections are produced by inoculation of infected blood. In this case the blood is immediately and continuously infective. This means that, as judged by blood infectiveness, there is a minimum incubation period of four days following injection of sporozoites, a minimum incubation period which cannot be reduced, however great the dose of sporozoites. When infected blood is inoculated, the incubation period is progressively reduced with every increase in dose.

As regards the merozoites resulting from the first and subsequent exoerythrocytic schizogonies, these vary in their disposition to enter other endothelial cells or the red blood corpuscles. In this respect they are "histotropic" or "haemotropic". In *P. relictum* the first merozoites are highly histotropic, so that the organs of birds examined soon after sporozoite infection reveal exoerythrocytic schizonts. The second and following merozoites are more haemotropic and possibly not histotropic at all, with the result that exoerythrocytic schizonts become increasingly difficult to find. This is true of *Haemoproteus* and presumably of *P. falciparum*. On the other hand in *P. gallinaceum* the successive batches of merozoites are highly histotropic, so that exoerythrocytic schizonts are readily detected at all stages of infection. It would seem that *P. vivax* and *P. malariae* occupy an intermediate position in this respect.

The author finally claims that he has demonstrated exoerythrocytic stages of development in *all* the three human parasites, chiefly in bone marrow taken by sternal puncture from patients a few days after infection by sporozoites. Only in the case of *P. malariae* has he been able to demonstrate such forms a year after infection had taken place. He notes that the existence of these stages affords an explanation of the failure of various drugs to prevent infection from sporozoites though the drugs are known to be active in the case of the erythrocytic stages of development. The author finally shows that the demonstration of

the exoerythrocytic forms in human malaria by himself and others establishes once for all the similarity of the human and avian parasites.

C. M. Wenyon.

León, A. P., Beltrán, E. & Larenas M., R. Acción del sulfalumín sobre los parásitos del paludismo experimental de los pollos, *P. gallinaceum.* [**Action of Sulfalumín on** *P. gallinaceum.*] *Rev. Inst. Salubridad y Enfermedades Trop.* Mexico. 1945, Sept., v. 6, No. 3, 137–43. English summary.

The authors have treated chickens infected with *P. gallinaceum* by blood inoculation with a drug called " Sulfalumin " (aluminium para-amino-benzene-sulphonate). It was administered orally twice daily in doses of 0·5 gm. per kilo. of body weight. When treatment was commenced during the incubation period (first to sixth day) the blood infection was prevented in most cases and clearly inhibited in the others. If treatment was delayed till parasites had appeared the results were less satisfactory. *C. M. Wenyon.*

TRYPANOSOMIASIS.

Eagle, H. **The Treatment of Trypanosomiaisis with *p*-Arsenosophenylbutyric Acid. I. Results in 319 Cases of Early** *Trypanosoma gambiense* **Infections.** *Pub. Health Rep.* Wash. 1946, July 12, v. 61, No. 28, 1019–34. [16 refs.]

Preliminary accounts have already appeared of laboratory and field trials of *p*-arsenosophenylbutyric acid against various forms of trypanosomiasis [this *Bulletin*, 1945, v. 42, 15 ; 354 ; 970]. The present is a more detailed report of results in cases of early *T. gambiense* infection. The data were obtained in collaboration with the Sleeping Sickness Services of the Belgian Congo, French Equatorial Africa, French West Africa, the Gold Coast, Nigeria, and the Firestone Plantation in Liberia.

For the purpose of this study, any patient with less than 10 cells per cmm. and less than 25 mgm. protein per 100 cc. was arbitrarily classified as "early", with a normal fluid ; patients with 10 to 20 cells were included only if the protein were less than 20 mgm. per cent. ; and patients with more than 20 cells were excluded.

Most of the patients received about 0·4 mgm. of the drug per kgm. per injection, but some received as little as 0·25 mgm. and others as much as 2 mgm. per kgm. (0·4 mgm. per kgm. is 1/65 of the maximal tolerated intraperitoneal dose for mice, 1/7 of the maximal tolerated intravenous dose for rabbits, and 1/19 of the intravenous LD_{50} for dogs). The total number of injections varied from 3 to 23 ; they were administered at various intervals :—daily ; three times each week ; twice weekly ; every 5 days ; weekly ; or at irregular intervals. Injection was usually intravenous, but very occasionally it was intramuscular ; in the latter event, contrary to experience with neoarsphenamine or mapharsen, there was either no reaction or there was transitory discomfort at the site of injection. Immediate or delayed toxic reactions were few and unimportant, though 2 of the 319 patients died of obscure causes within a week after the end of treatment.

About two-thirds of the total were observed for less than 6 months, and practically all the remainder for 6–12 months. At total dosages of 3·5, 3·5 to 4·9, 5·0 to 6·4, and 6·5 or more mgm. per kgm., the crude failure-rates, uncorrected for varying periods of observation, were 26, 10, 8, and 4·5 per cent., respectively.

The author concludes that more than 90 per cent. of early cases may be cured within 2 weeks by 12 to 14 daily injections of 0·5 mgm. of the drug per kgm., or within 1 week by 6 or 7 injections of 1 mgm. per kgm. Where daily treatment is not feasible, the same number of injections may be given at any desired interval, up to 1 week apparently, with equal therapeutic efficacy.

E. M. Lourie.

RIDLEY, H. **Ocular Lesions in Trypanosomiasis.** *Ann. Trop. Med. & Parasit.* 1945, Oct. 10, v. 39, No. 2, 66–82. [51 refs.]

[This is a review of the second part of the paper by Ridley, the first part of which has been dealt with in this *Bulletin*, 1946, v. 43, 534.]

In the second part of this paper, Ridley deals with the visual disturbances due to treatment with arsenical preparations. Probably in no other country is so much pentavalent arsenic used as in West Africa. Trivalent arsenical preparations are less toxic, but have the disadvantage that they do not penetrate the meningeal barrier and enter the central nervous system. Pentavalent compounds, chiefly tryparsamide (tryparsyl) and atoxyl (soamin), are therefore employed in trypanosomiasis as well as in cerebrospinal syphilis, which is also widespread in West Africa. These compounds are inactive *in vitro* and so a chemical change must take place in the tissues, liberating some reduced form of the drug which is the active parasiticide. After parenteral injections of tryparsamide, the cerebrospinal fluid becomes lethal to trypanosomes, but the effect is not in direct proportion to the total arsenic content. The precise mechanism of these drugs is not yet fully understood, but it is recognised that the use of organic arsenic, particularly in pentavalent form, carries certain risks. The chief of these is damage to the retina and visual pathway, as well as more rarely generalized toxic effects, resulting in jaundice, skin disorders, encephalopathy and even death.

Disturbances in vision develop in four stages. Firstly, the condition is entirely subjective, the patient complaining of metamorphosia and a sensation of shimmering movement which has been compared to looking through waving smoke. Secondly, within a few days objective phenomena appear, for there is a general depression of vision, with loss of the peripheral field for even large objects, followed by a marked diminution in central acuity. The appearance of the optic disks still remains normal. Thirdly, after an interval of about two weeks, pallor, unaccompanied by swelling or by vascular abnormalities, appears in the optic disks, and the patient may become completely blind, having inactive, 3/4 dilated, pupils. Fourthly, comes the stage of recovery, which may proceed for 3–6 months, in which there may be complete return of central acuity, accompanied by some degree of improvement in the peripheral fields. The pallor of the disks remains unchanged or may even progress, the retinal vessels—especially the arteries—become somewhat constricted, secondarily no doubt to degeneration of the retina itself, and white perivascular cuffing appears around the larger vessels near the optic disks. Acuity of even 6/5 is, however, compatible with almost complete pallor of the disks, but in such cases gross limitation of the fields will be found. In some cases recovery does not occur, the patient becoming permanently incapable of perception of light ; the pupils are inactive and 3/4 dilated, and the fundi show complete primary optic atrophy, with constricted vessels and perivascular cuffing.

Not all patients who have been poisoned by organic arsenic suffer severe and permanent visual damage. They may be divided into three groups : those with purely subjective and evanescent symptoms ; those who end with a moderate degree of visual impairment and optic atrophy ; and those in whom blindness is total and permanent and optic atrophy complete.

Tryparsamide is by far the most widely used pentavalent preparation of arsenic, and the author points out the importance of using only the freshest and purest preparations. " It is no exaggeration to state that it is possible that tryparsamide itself in normal dosages is a completely safe drug and that all the tragedies associated with its use are due to impurities."

It also requires, to the highest degree, care in preparation and use. It is the duty of the manufacturer to remove all impurities and to arrange that the interval between manufacture and administration is as short as possible. The user must ensure first and foremost that the drug is fresh and that it has been stored in a cool place, and further that the solution is made up with distilled, preferably double distilled, water. As most of the inhabitants of the African bush are undernourished, the injections of tryparsamide might be supplemented with glucose and other concentrated foods to build up the patient's strength. Dosage must be carefully adjusted to general physical condition and weight. The treatment of patients who have visual disorders requires special mention. Tryparsamide is naturally discontinued as soon as there is evidence of toxic reaction, and it is unwise even after an interval, to administer further pentavalent arsenic, though a choice may have to be made between blindness and death. Before ophthalmic treatment is begun, ophthalmic precautions such as complete examination of the eyes, including the visual fields, should be carefully and accurately done, and the patient must be warned to report even the slightest visual disturbance immediately. *E. O'G. Kirwan.*

HAVEAUX, G. Vingt ans d'action médicale contre la maladie du sommeil dans le Kasaï. [**Twenty Years of Sleeping Sickness Control in the Kasaï.**] *Ann. Soc. Belge de Méd. Trop.* 1945, Dec. 31, v. 25, Nos. 3/4, 155–203, 3 figs.

This is a detailed account of the sleeping sickness activities of the mining group known as the *Société Forminière*, in the Kasaï region of the Belgian Congo, during 20 years up to 1943, at a cost of 9,174,741·06 francs.

A medical survey by Dr. GILLET in 1922 revealed important endemic foci at Tshikapa, the African headquarters of the " Forminière " (1 to 5 per cent. infection-rate), and at Dibaya, not far from Bakwanga (10 per cent. infection-rate). A general medical and sanitary service was organized by the Society the next year, and this was followed two years later by a separate organization, the M.P.M.S. (*Mission de Prophylaxie contre la Maladie du Sommeil*), whose activities were to cover the greater part of the Kasaï district. Arrangements were made for close collaboration with the government medical services, and the report describes the fluctuating allocation of responsibilities and operational zones, as between the respective organizations of the " Forminière " and the government. Examples are given of some of the directives issued by the Society at different times to its sleeping sickness " agents ", each of whom was responsible for the examination of about 50,000 persons per annum.

Three distinctive periods are recognized during the 20 years under review. The first, 1923 to 1925, was occupied by general preliminary organization and installation, and the second, from 1926 to 1931, by considerable extension and mass treatment. The third period dates from 1932, when the service was reorganized in the light of experience gained, and a number of improvements were introduced, such as the examination of cerebrospinal fluid as a routine procedure for diagnosis and follow-up. The number of persons examined per year varied between about 100,000 and 150,000, except in 1923–5, 1937, 1940, 1941 and 1944, when the number varied between about 30,000 and 80,000. A table is given to show the numbers examined, the numbers of new and old patients respectively, and the numbers of lumbar punctures performed, year by year.

The report details the work of the M.P.M.S. during each of the three periods mentioned above. During the first period patients were treated (subject to the variable factor of their co-operation) by 1 cgm. of atoxyl per kgm. on three successive days, during which they were to accompany the itinerant control teams ; this was followed by two or three similar courses of daily injections, at intervals of at least eight days. The first examinations in the Batshok region disclosed an important focus with a 10 per cent. infection-rate between the Rivers Lovua and Tshikapa, near the Angola frontier, the incidence diminishing from here towards the East and the North. The general infection-rate, among both the non-immigrant population and the Forminière's labourers and their families, was found to be about 2 per cent. at the beginning of this period, falling to 0·83 per cent. in 1925.

In the second period special efforts were at first directed towards the zones of high infection, reaching to 10 per cent. in some villages in the neighbourhoods of Dibaya and Luluabourg. During this period the dosage of atoxyl, in cases where this was used, was increased to a total of about 6 gm. per patient, but tryparsamide (tryponarsyl) gradually took the place of atoxyl, in a dosage of 12 gm., in six injections at weekly intervals. Later the customary dose was increased to 24 gm., in 12 injections at weekly intervals. An account is given of the number of patients examined and the infection-rate, together with other local details, sector by sector, and year by year, during this period.

The most detailed part of the report concerns the third period, from 1932 to 1943, and this is divided into chapters under the headings of :—*Census-taking ; Diagnosis ; Treatment ; Follow-up ; Preventive treatment ; Results Sector by Sector.*

Census-taking.—Great pains were taken to maintain accurate census records, since this was rightly regarded as indispensable to success. Census-taking was apparently a responsibility of the "agent sanitaire", and not of an administrative officer.

Diagnosis.—The routine in highly endemic regions varied slightly from that adopted in less heavily infected places. The various procedures are described, and are similar to the well-known methods used by sleeping sickness organizations in other parts of West Africa.

The cerebrospinal fluid cell-count-distribution was found to be fairly constant among new cases examined in different areas, though there was a tendency in any given zone for the percentage of new cases of the 80–200 cells per cmm. category to increase over a long observation period, as for example in one zone where these cases increased from about 2 per cent. to about 7 per cent., over a period of six years. A typical cell-count-distribution among new cases is the following, obtained from 383 cases in 1933, in a region where the infection-rate was 0·46 per cent. :—0–3 cells, 26 per cent ; 3–20 cells, 57 per cent. ; 20–80 cells, 11·5 per cent. ; 80–200 cells, 2 per cent. ; over 200 cells, 3 per cent.

Treatment.—This did not follow a rigid rule, and was administered in centres where patients were admitted to hospital, the main centre being at Tshikapa. The following was the general pattern adopted :—

(1) *Patients in good general condition, with cell-counts less than* 80 *per cmm.*—Per 50 kgm. body weight : one or two injections of 1 gm. Bayer 205 (moranyl, belganyl), followed by six injections of 3 gm. tryparsamide. (Children aged 5–10 years, 9 cgm. per kgm., aged 10–15 years, 7 cgm. per kgm. ; adults, 6 cgm. per kgm.)

(2) *Patients in poor general condition, and those with cell-counts above* 80 *per cmm.*—The injection-dose of tryparsamide in these cases was reduced to 4·5 cgm. per kgm., to minimize the possibility of ocular damage. Courses consisted of 12–15 injections.

(3) *Chronic cases or those with a specially bad prognosis.*—These were treated by a variety of combined courses of tryparsamide, Bayer 205, or tartar emetic, in moderate or small doses for prolonged periods, in the hope of establishing a *status quo ante*, if not a cure.

(4) *Cases resistant to arsenicals.*—Such cases were found to be very rare since adoption of the practice of administering the treatment-courses in centres of hospitalization. They were given 12 injections of tryparsamide, in moderate dosage, combined with 6 to 10 injections of Bayer 205 and tartar emetic, "if necessary". [It is not apparent why tryparsamide should be given in this way, "*à doses moyennes*", to arsenic-resistant cases.] There is less danger of ocular damage here, since 95 per cent. of these patients have low cell-counts. An increased cell-count in this type of case after a long period of stability often heralds the end. The tryparsamide was given in 30 per cent. solution, in 10 per cent. sodium thiosulphate in doubly distilled water; toxic effects of treatment were very rare. Where ocular damage supervened, treatment was suspended and injections of 20 per cent. sodium thiosulphate administered until vision improved, when arsenicals were again cautiously resumed.

Follow-up.—Patients were re-examined, including investigation of the cerebro-spinal fluid, every year for five years. If in good condition, with a c.s.f. cell-count not above 5 per cmm., they were then classified as "Apparently Cured", and kept under observation for a further period of five years, with complete re-examination on the slightest suspicion of relapse. At the end of the total of 10 years, a final lumbar puncture was performed, and if no abnormality was found the patient was then pronounced "Definitely Cured". The percentages of patients found to be cured each year are set forth in a table, and grouped according to the duration of time since treatment. For example, in 1942, out of 1,172 patients who presented themselves for follow-up, the percentage of cures (as a ratio of cases actually re-examined) were as follows:—first follow-up (1 year after treatment), 80 per cent.; second 87·1 per cent.; third 93·1 per cent.; fourth 98 per cent.; fifth (5 years after treatment), 95·6 per cent.; final follow-up (10 years after treatment), 99·1 per cent. [Baldly stated, the cure-rate of 99·1 per cent. seems an excellent result. For some years a cure-rate of even 100 per cent. is quoted. It must be borne in mind, however, that patients who relapsed and then died or failed to appear for re-examination are excluded from the reckoning.]

A special study was made of 118 patients closely followed up for 10 years. The results are analysed and recorded in tables according to age-group and c.s.f. cell-count at the start of treatment. A 9-page appendix to the report gives the case-histories of every one of these 118 patients. There were 108 with initial cell-counts of 0–80, and 10 with initial counts of more than 80 per cmm. Of these two groups, 83·3 per cent. and 80 per cent., respectively (as ratios of the totals treated), were cured at the end of the ten-year period. Broadly, the age-distribution of the 118 patients was: 1–10 years, 7 cases; 10–45 years, 103 cases; over 45 years, 8 cases; and the annual death-rates in these respective groups were 0 per cent., 1·4 and 50 per cent. Among the general population the death-rates per annum in the Bas-Congo, for the two older age-groups, were 1·2 and 5 per cent., and the figures therefore demonstrate, in the author's view, that sleeping sickness is easily cured in young people or in those in prime of life, but not in older persons, under local conditions.

Preventive treatment.—This involved one injection, or preferably two or three at weekly intervals, of 1 gm. Bayer 205, administered to everybody, after curative treatment of those found to be infected. There were three cases of fatal syncope in the course of these preventive injections, *i.e.* a mortality of 1 per 10,000. Full details of this particular work have already been published by

Fourche & Ricklin [this *Bulletin*, 1929, v. 26, 193] and Fourche & Haveaux [this *Bulletin*, 1932, v. 29, 305]. Further details are given in the present report. The duration of protection was judged to be about 6 months.

Results Sector by Sector.—Separate detailed accounts, covering 10 pages of text, are given of the work done in each of nine geographical sectors. These do not lend themselves to summary. References are made to population-displacements found to be necessary in several zones of the Tshikapa Lutshiko sectors.

In an interesting concluding section the author outlines the way in which mass movements of populations, due to dynastic quarrels, inter-tribal warfare, railway and industrial developments, etc., have conduced to the spread of sleeping sickness. Apparently the infection has converged upon Tshikapa, through these population-movements, both from the west and from the East.

From the west came the Bampende, from the River Kwango, installing themselves in the lands of the long-settled lesser tribes, and other important invaders were the Lunda. Not long before the arrival of the Europeans a further wave swept over from the west ; the warlike Batshok, "*les prussiens de l'Empire*," kinsmen and rivals of the Lunda, burst into the Kasaï, enslaving the populace, except for the Bampende, who recoiled before the invasion, and it is this movement of the Batshok, in particular, to which the author ascribes the spread of infection from the Kwango into the Kasaï, which was recognized in 1923.

Well over to the east, on the banks of the Bushimai and the Lomami, and beyond, the first Europeans put an end to the internecine warfare of the Baluba, but ineradicable hatreds and rivalries remained. In order to ensure the authority of the Chiefs recognized by the State, it became necessary to separate the dissident groups. They were moved westward, first to Luluabourg, then to Luebo, Tshikapa, etc. This was the first wave of infected Baluba tribesmen towards the Kasaï. The subsequent building of a railway in the Dibaya and Luluabourg territories gave rise to further population-shifts, with still further spread of sleeping sickness into these particular areas, from which infection was brought into Tshikapa by the recruitment of labourers.

[There are no detailed references to tsetse flies, or to tsetse fly control, in this report.] *E. M. Lourie.*

McLetchie, J. L. **The Control of Sleeping Sickness in Northern Nigeria.** *Farm and Forest.* Ibadan, Nigeria. 1945, Apr.–June, v. 6, No. 2, 69–79.

The Anchau Settlement in the Zaria and Kano Provinces of Northern Nigeria has previously been mentioned in this *Bulletin*, but the account given by the present author is the first seen by the reviewer in which the administrative details have been fully described. The settlement was conceived as part of the scheme for the control of trypanosomiasis, in view of the fact that control by mass treatment, although highly successful, could not be regarded as a final answer to the problem, in that it seemed impossible by that method alone completely to eradicate the human disease ; moreover, mass treatment was not applied to cattle. The area of the Settlement was chosen because it seemed probable that complete eradication of tsetse could be achieved and maintained by an effort not beyond the capacity of the population ; the corridor which will eventually be rendered free from fly is about 70 miles in length and comprises 700 square miles. In this corridor the people from surrounding (and infested) districts are, or will be, concentrated ; they will be protected from fly, but the fact of concentration and removal to strange surroundings must inevitably introduce new problems, medical, veterinary, agricultural and social. All these

problems must be solved ; many were anticipated and provided for, but others could not be foreseen.

The work was started in 1937, with a grant from the Colonial Development Fund of £95,000 to be spread over five years, and during the same period the Nigerian Government proposed to increase expenditure on the treatment service by £55,000. The tsetse control staff included 14 Europeans—two entomologists, one District Officer, one well-sinking foreman, and ten Control Officers. The scheme was controlled by the Sleeping Sickness Service, but a committee from all the departments concerned was created to advise on policy. [Dr. McLetchie wishes it to be made clear that Dr. H. M. O. LESTER was primarily responsible for the conception of the Anchau scheme, and that in the early years of development Dr. T. A. M. NASH was in local charge at Anchau.]

In 1938 and 1939 the preparatory work was initiated, basic investigations were made, and staff was trained. In 1940 and 1941 movements of the population were made into the Settlement, and clearings were extended. Thereafter, because of the war, the work was placed on a maintenance basis until, later in 1942, there was a gradual resumption of tsetse surveys, research, clearing, well-sinking and general development.

The amount of work done is indicated in the body of this paper, but the great difficulties always met in any attempt to change the habits and customs of an intensely conservative people are hinted at rather than stressed. The peasants are Moslems ; some lived in reasonably prosperous villages, but many were on a bare subsistence level and were not good farmers. Guineaworm infection was rife and contact with tsetse very close. It was necessary to assess the fertility of the land to which the people were to be moved, a difficult task since no accurate scientific method of assessment for this area was known. Nevertheless, a pointer was recognized by an Agricultural Officer, which was the presence of certain trees, and the density of growth of grass. Certain plots were cleared, and four stable crops planted in each ; growth and yield were correlated with soil and vegetation types, and the association of the trees mentioned above, with fertile soil, was established. New village sites could now be chosen, after extensive survey and mapping had been done. Land was divided among the householders, according to native practice, by the headmen of the hamlets. Compounds were dispersed singly or in groups ; the layout now advised is a group of houses round a central well-space, 100 feet square. The compounds themselves are 100 feet square, and are separated from each other by a space of 100–125 feet. Huts are 12 feet in diameter, and 12 feet apart.

In the first period the technique of stream clearance was standardized, and over 300 miles of stream were cleared. Within the Settlement area streams are partially cleared, mahogany and other valuable, high-branching trees being left at intervals. " To prevent re-infestation of these streams by tsetse from the uncleared rivers outside the corridor, a ' barrier ' clearance straddles the corridor boundary. The barrier is a mile in length, 50 to 100 yards broad, and is cleared ruthlessly."

The sinking of wells, and the protection of well-heads, was carried out on a large scale. Fruit trees and other sources of foodstuffs were introduced, and the disposal of rubbish and animal manure was given attention.

In the dry seasons of 1940 and 1941 the major population movements were made, water supplies were improved, and anti-tsetse clearances were extended. By the second year, 16 new villages and seven extensions to existing villages, were completed. Pit latrines were introduced to all compounds, and the authorities insisted on their use and care. The value of a combination of partial and barrier clearance was now proved, and clearing was therefore extended. The organization of annual re-slashing of already cleared areas was even more

laborious than initial clearing ; this is done on a communal basis, and requires about four days' work from each adult male. " Villagers re-slash well, the more sophisticated people of large towns badly." Moreover, people from the slums of old Anchau did not cooperate well, and were poor farmers. Experiments with new crops were made and continued, and an estimate of fuel requirements (15 cwt. of wood per person each year) was made, and fuel areas, calculated accordingly, were marked out.

Cotton and ground-nut markets were opened, the preparation of hides for export was taught, soya cultivation was introduced and sugar production encouraged. Cattle were inoculated against rinderpest, but trypanosomiasis interfered seriously with the cattle programme ; this disease was transmitted, not by tsetse, but by other blood-sucking flies. Fodder for livestock became scarce, but arrangements were made to cultivate it.

By the end of 1942 the people had accepted their new life cheerfully, but continued supervision was very necessary. After that the programme of expansion, in abeyance for 18 months, was resumed, and improvements were made within the corridor. A demonstration farm was opened and schools were started in all districts and in many villages.

The only human diseases mentioned in this paper are cerebrospinal meningitis, smallpox, guineaworm and trypanosomiasis. Outbreaks of the first two occurred but were controlled, and the value of treatment for meningitis, and of vaccination for smallpox, are apparent to the people. Guineaworm, which creates havoc in parts of Nigeria, will presumably be controlled as good wells come into use, and human trypanosomiasis will not be a problem so long as anti-tsetse measures are maintained. Mosquito breeding is mentioned but not discussed.

[The Anchau settlement is the biggest concentration of population yet made in Africa, and offers, perhaps, the best opportunity for introducing to the African a mode of life far more beneficial than anything he has yet known, but it seems evident that supervision will be needed for many years ; to expect of the African a rapid abandonment of conservatism would be unwise. It is necessary to take a long view.] *Charles Wilcocks.*

CLARKE, J. D. **Pattern for Progress in Rural Africa.** *Oversea Education.* 1946, Apr., v. 17, No. 3, 295–301.

This account of the Anchau Corridor gives much the same information as is given by MCLETCHIE (above), but adds emphasis on some of the points. The author notes with approval the fact that when the scheme was first mooted as a measure of control of trypanosomiasis, the medical authorities were not content that it should merely offer protection against that disease, but decided, in collaboration with other departments, that the whole area should be developed in the economic and social sense, and that an advanced degree of rural hygiene should be encouraged. The population aimed at was not less than 70 to the square mile, at which communal clearing is possible.

The new villages are now most attractive, and people from outside the area apply to be allowed to settle in them. In these rural schemes there has been a mixture of compulsion and persuasion ; in the opinion of the Control Officers the people appreciate the new way of life, but need supervision to ensure that the present high standards are maintained. One of the most important activities is the education of the people themselves, in the small schools which have been instituted ; this is not education reserved for the few who show promise, but simple instruction for the many, who may, because of it, be influenced towards the desire for better conditions than they have demanded in the past.

So far the scheme has cost £15,000 per annum, which represents 5s. per head of the population affected. The maintenance cost will now be reduced to one-fifth of these figures. Such expenditure is obviously worth while, in terms of the health and welfare of the people. "Anchau is not merely a method which ought to be widely used in the control of endemic disease; it is an example to all departments of government."

The author was "cheered by the sight of a job well done; it was refreshing to visit a scheme which has been carried out without counting the pence, and which has therefore been a success." *Charles Wilcocks.*

AUGUSTINE, D. L. **Some Factors in the Defense Mechanism against Reinfection with** *Trypanosoma lewisi.* Reprinted from *Proc. Amer. Acad. of Arts & Sciences.* 1943, May, v. 75, No. 3, 85–93, 5 figs. on 1 pl. [10 refs.]

The author has studied the mechanism of immunity of rats to reinfection with *Trypanosoma lewisi* by examining the peritoneal fluid, the lymph nodes which drain this fluid, and the blood, after intraperitoneal inoculation of large numbers (200–900 million) of trypanosomes. It was demonstrated that the trypanosomes passed as readily through the lymph nodes to the blood in rats which had recovered from a previous infection as in rats which had had no previous infection. In recovered rats, however, the trypanosomes arriving in the blood were rapidly removed within a few minutes to four days. The length of time of survival depends upon the titre of the antibody and the stage of development of the trypanosome in the blood. Dividing trypanosomes are almost immediately sensitized by the antibody, being either killed or immobilized and are finally phagocyted by blood macrophages. Adult trypanosomes are more resistant, and survive till the titre of the antibody reaches a point at which they are agglutinated into masses of living trypanosomes which are filtered from the blood in the internal organs, where they are destroyed. The fact that the trypanosomes in the blood may commence dividing shows that any ablastin remaining from the first infection, which functions by stopping reproduction, is inactive and plays no part in the immunity to reinfection. This immunity is dependent upon a humoral trypanocidal antibody to which developing parasites are particularly susceptible and adult parasites relatively resistant. *C. M. Wenyon.*

LAUNOY, L. & LAGODSKY, H. De l'action préventive d'une diamidine aromatique : la diamidino-diphénoxypentane, sur deux trypanosomoses expérimentales du rat. [**The Preventive Action of an Aromatic Diamidine (Diamidino-diphenoxypentane) on Two Experimental Trypanosome Infections in Rats.**] *Bull. Soc. Path. Exot.* 1946, v. 39, Nos. 5/6, 160–67.

LAUNOY, L. & LAGODSKY, H. Nouvelle contribution à l'étude de l'action préventive de la diamidino-diphénoxypentane sur les infections expérimentales à *T. brucei* et à *T. evansi* du rat et du lapin. [**Observations on the Preventive Action of Diamidino-diphenoxypentane on Experimental Infections with** *T. brucei* **and** *T. evansi* **in Rats and Rabbits.**] *Bull. Soc. Path. Exot.* 1946, v. 39, Nos. 5/6, 197–200.

SCHATZ, A., MAGNUSON, H. J., WAKSMAN, S. A. & EAGLE, H. **Isolation of an Antibiotic Agent derived from a** *Phycomyces* **Active** *in vitro* **against** *Trypanosoma equiperdum. Proc. Soc. Exper. Biol. & Med.* 1946, June, v. 62, No. 2, 143–5.

"Several soil fungi have been found to produce filtrates active against *Trypanosoma equiperdum.* From a *Phycomyces* sp. a lipid-like substance was

isolated which immobilized the trypanosome *in vitro* but exerted no protective action against the experimental infection in mice.

"No inhibitive agent has heretofore been obtained from this group of fungi. The selective action of the phycomyces factor against the trypanosome, but not against bacteria, is of particular interest."

LWOFF, M., Mme. & NICOLLE, P. Recherches sur la nutrition des réduvidés hémophages. V. Alimentation de *Triatoma infestans* Klug à l'aide de sérum vitaminé. Importance de l'acide pantothénique. [**Studies on the Nutrition of Blood-sucking Reduviidae. V. Feeding of** *Triatoma infestans* **by means of Vitaminized Serum. Importance of Pantothenic Acid.**] *Bull. Soc. Path. Exot.* 1946, v. 39, Nos. 5/6, 206–21, 9 figs. [18 refs.]

DAVIS, D. J. & SULLIVAN, Thelma de S. **Complement-Fixation Tests for American Trypanosomiasis in Texas.** *Pub. Health Rep.* Wash. 1946, July 19, v. 61, No. 29, 1083–4.

Complement-fixation tests, in which *T. cruzi* antigen was used, were carried out on (1) 1,909 samples of serum, of which 568 were from persons who lived largely in shelters harbouring triatomid bugs; (2) 1,002 Kline-negative samples, chiefly from counties where *T. cruzi* had been demonstrated in insects; and (3) 339 samples which had been negative to ordinary routine clinical diagnostic tests.

The only serum found to fix complement in a significant dilution was from an 8-year-old boy living in a neighbourhood where many specimens of *Triatoma gerstaeckeri* had been found to be infected with *T. cruzi*. No further evidence that he was infected was obtained by clinical examination or animal inoculation. *H. J. O'D. Burke-Gaffney.*

DUBOIS, C. **Chimiothérapie des trypanosomiases.**

This book is reviewed on p. 1087.

LEISHMANIASIS.

NÁJERA ANGULO, L. Hallazgo de "Phlebotomus" en Galicia y consideraciones sobre la epidemiologia de las leishmaniosis. [**Finding of** *Phlebotomus* **in Galicia. Epidemiology of Leishmaniasis.**] Reprinted from *Bol. de la Real Soc. Española Hist. Nat.* Madrid. 1945, v. 43, 25–30, 2 figs.

The author discusses the distribution of sandflies in the various provinces of Spain in relation to the existence of leishmaniasis visceral or cutaneous. He shows that recent observations have disclosed sandflies, chiefly *Phlebotomus perniciosus*, in certain provinces, even to a height of 1,500 metres, where their presence was previously unrecorded. These observations reduce the number of provinces in which both sandflies and leishmaniasis have not been demonstrated and it seems probable that careful observations by both clinicians and entomologists will fill the lacunae. The author shows in a map how close is the correspondence between the distribution of sandflies and leishmaniasis.

C. M. Wenyon.

AKALIN, M. S. Anadolu Flebotomlari. [*Phlebotomus* **in Anatolia.**] *Türkische Ztschr. f. Hyg. u. Exper. Biol.* Ankara. 1941, v. 2, No. 2, 113–26, 4 figs. German summary 127.

The following species were found:—*P. papatasi*, *P. perniciosus*, *P. minutus*, and *P. sergenti*.

PACKCHANIAN, A. **The Distribution of Species of Sandflies, Genus *Phlebotomus*, in the United States and their relation to the Transmission of Leishmaniasis.** *Texas Reports on Biol. & Med.* 1946, v. 4, No. 1, 35–41. [21 refs.]

NÁJERA ANGULO, L. La existencia de lesiones cutáneas en la leishmaniosis visceral mediterránea y su significación epidemiológica. [**Epidemiological Significance of Cutaneous Lesions in Kala Azar.**] Reprinted from *Rev. Clín. Española.* 1945, July 15, v. 18, No. 1, 28–37, 4 figs. [12 refs.] French summary.

Having encountered a case of kala azar in Spain in a boy who was suffering at the same time from ulcers on the lower lip and leg (in which, however, leishmania could not be demonstrated) the author discusses the world distribution of kala azar with particular reference to the disease as seen in Southern Asia and the Mediterranean region. He believes that from the point of view of the tendency to cutaneous ulceration, and other lesions, of other specific characteristics, and of the co-existence of canine kala azar, this area is divisible into three zones separated by a line running from a point just west of the Crimea to the northern end of the Red Sea and another line running down the Adriatic and crossing the Mediterranean. [It is not always easy to see on what grounds the conclusions are based, nor the reason for introducing the subject of oriental sore, which is discussed to some extent.] The author's view is that knowledge of these subjects is most imperfect and that it is of the utmost importance that there should be carried out a co-ordinated investigation in the three zones, centred on Pasteur Institutes in Algiers, Athens and Baku.

C. M. Wenyon.

PINTO, H. Notícia acêrca de 40 casos de " kala-azar " registados da consulta do pôsto anti-sezonático do Pocinho em 1943. [**Forty Cases of Kala Azar found by the Anti-Malarial Organization at Pocinho, Portugal, in 1943.**] *Sezonismo.* Lisbon. 1944. (Trabalhos originais-1943.) 43–5.

NÁJERA ANGULO, L. Criterio diagnostico en la leishmaniosis visceral mediterranea. [**Diagnosis of Mediterranean Kala Azar.**] 52 pp., 18 figs. [Bibliography.] 1946. Madrid.

In this article the author discusses the various procedures and techniques which have been employed in the diagnosis of kala azar, basing his remarks on cases of the infantile disease seen by him in Spain. He concludes that the only reliable criterion is the discovery of the parasite itself by puncture of a lymphatic gland, the bone marrow or the spleen ; the operations are carried out in this order, the later ones being undertaken only when the earlier ones have failed. He again refers to the presence of his supposed " schizogony forms " of the parasite in the bone marrow, believing that the leishmania in other situations are merely phagocyted organisms destined to destruction. Actually, the article gives no new information of importance. *C. M. Wenyon.*

COOPER, G. R., REIN, C. R. & BEARD, J. W. **Electrophoretic Analysis of Kala-azar Human Serum. Hypergammaglobulinemia associated with Seronegative Reactions for Syphilis.** *Proc. Soc. Exper. Biol. & Med.* 1946, Feb., v. 61, No. 2, 179–83, 1 fig. [27 refs.]

" The electrophoretic patterns of 2 human kala-azar sera revealed the presence in high concentration of a unique, abnormal component migrating with the γ globulin of the slowest mobility. The kala-azar sera, negative to serological tests

for syphilis, provide instances which show that the presence of hyperproteinemia, hyperglobulinemia or hypergammaglobulinemia cannot be used to prove or disprove the specificity of positive serologic reactions for syphilis."

SAGHER, F. **Activation of an Originally Negative Intracutaneous Leishmania-Vaccine Reaction.** *Acta Med. Orientalia* (*Palestine & Near East Med. J.*) 1946, Mar., v. 5, No. 3, 82–5, 2 figs.

In the vast majority of cases of cutaneous leishmaniasis, as shown by DOSTROVSKY, the injection into the skin of a leishmania vaccine containing 100,000 culture forms of the parasite in 0·1 cc. is followed by a positive reaction, characterized by redness over an area 3 cc. in diameter, and a central papule. In certain cases which show little tendency to spontaneous healing and which prove very resistant to treatment, the reaction is negative. These are often relapse cases, in which a lupus-like condition commences in the margins of an apparently healed sore. In a case described in this paper practically the whole of the right cheek became involved. Treatment by X-rays on a number of occasions failed to induce healing. The skin reaction at this time was negative to vaccines prepared from Palestine and Baghdad strains of leishmania. Treatment with grenz-ray was then given, with the result that healing commenced. At the same time the skin reaction became slightly positive. Complete cure eventually resulted after a period of three years. When healing was complete the skin reaction was strongly positive to both vaccines. The author considers it possible that the failure of such cases as the one described, to show any tendency to spontaneous recovery, is due to lack of development of antibody, and that it is the lack of this antibody which causes the skin reaction to be negative. With development of antibody, healing commences and the reaction becomes positive. On the other hand, the reaction may be due to an increased allergy or hypersensitivity having no relation to immunity. In either case it is not clear how the institution of treatment by grenz-ray could bring this about.

C. M. Wenyon.

BOSE, A. N., GHOSH, T. N., MITRA, S. N. & DATTA, S. **On the Toxicity of some Organic Antimonial Drugs used for the Treatment of Kala Azar.** *Indian Med. Gaz.* 1946, Jan., v. 81, No. 1, 13–16.

It is well known that organic antimonials employed in the treatment of kala azar vary considerably in toxicity from batch to batch. This is particularly the case with derivatives of *p*-aminophenylstibinic acid such as urea stibamine (the exact composition of which is still uncertain), the diethylamine salt (neostibosan) the tri*iso*propylamine salt and others. With a view to throwing light on these variations in toxicity a number of different batches of these preparations were studied from the point of view of their total antimony content, and the various combinations in which this antimony was present. At the same time, toxicity tests were carried out in mice. It was found that, though the toxicity of urea stibamine generally increased with a rising antimony content, it was clear that this was not the sole cause, as certain samples with high antimony content were less toxic than others with a lower content. An explanation was found in the presence of antimonious acid. If the ratio of antimony present as antimonious acid to that present in pentavalent organic combination exceeds 1 : 26 there occurs a definite increase in toxicity. If care is taken, in the preparation of urea stibamine, to keep the ratio low, it will satisfy much higher toxicity limits than those at present accepted (namely 200–225 mgm./kgm. intravenously). As regards the other compounds studied, the di-ethylamine, and the *iso*-propylamine salts, their toxicity depends largely

on impurities in the amines employed in their preparation. There was also some indication that the toxicity of the di-ethylamine salt could be reduced by incorporating a minute trace of a suitable reducing agent.

C. M. Wenyon.

Dutta, N. K., Mukerji, B. & Sekar, C. C. **The Possibility of using Pigeons in Toxicity Determinations of Organic Antimony Compounds.** *Quart. J. Pharm. & Pharmacol.* 1946, Apr.–June, v. 19, No. 2, 89–96, 2 figs.

Since white rats and mice are not freely available in all parts of India, the use of pigeons has been suggested for determining the toxicity of organic compounds of arsenic and antimony. The common Indian pigeon (*Columba livia intermedia*) is found all over the country and can be obtained at reasonable cost. It is easily handled and is not exacting in its requirements. These birds, kept under good conditions in groups of four, were used, in conjunction with chemical tests, for the assay of urea stibamine. A freshly prepared 4 per cent. aqueous solution was given into a wing vein. Not less than twenty pigeons were inoculated at a time and the period of observation was one week. For the purpose of comparison, parallel toxicity tests on the same batch of drug were carried out with mice. From analysis of the results obtained in the two series of tests, it was concluded that under the conditions employed, the use of pigeons for bio-assay was justified.

J. D. Fulton.

Oastler, E. G. & Fidler, H. K. **Cerebral Lesions produced in Healthy Dogs by the Intravenous Injection of 4 : 4′-Diamidino Stilbene.** *Trans. Roy. Soc. Trop. Med. & Hyg.* 1946, June, v. 39, No. 6, 533–8, 5 figs. (4 on 1 pl.)

In this paper are described certain lesions of the central nervous systems in dogs following the intravenous injection of freshly prepared solutions of stilbamidine. The experiments were undertaken because of observations made on cases of kala azar treated with old solutions of stilbamidine which had been exposed to light. A number of dogs treated with the same old solutions showed pathological lesions in liver and kidneys. It is now well known that under the above conditions stilbamidine solutions undergo photochemical change [this *Bulletin*, 1943, v. 40, 23, 683, 684 ; 1944, v. 41, 196 ; 1945, v. 42, 18]. When freshly-prepared solutions were administered to 10 other dogs, significant pathological lesions occurred only in the c.n.s., and were associated with definite clinical signs, especially spasticity. The lesions described in the text included infiltration and thickening of the walls of blood vessels, myelin degeneration, softening, inflammation of the meninges, as well as haemorrhage and thrombosis. Nervous disturbances have previously been described in man and animals treated with members of the diamidine series [this *Bulletin*, 1940, v. 37, 404 ; 1942, v. 39, 748 ; 1944, v. 41, 273]. The dosage schedule for the dogs was 1, 1·5 and 2 mgm. per kilo. of body weight given intravenously each day during the first, second and third weeks respectively. From 4 to 21 injections were given in the series before the animals died or were killed. Five of them showed clinical signs indicative of damage to the c.n.s., which was verified *post mortem*, but its degree was apparently unrelated to the amount of drug given. Three other animals had no brain lesions, while in the remaining two the damage was microscopic. Foci of necrosis occurred in the liver of one dog, and others had slight fatty degeneration of the kidneys. The cerebral lesions were believed to result from vascular spasm or anoxia ; and in view of the neuropathic signs noted in human cases after treatment with diamidines, this probably does not represent a special susceptibility in the case of dogs.

J. D. Fulton.

MUKERJEE, S. **Penicillin for Isolation of Bacteria-Free Culture of *Leishmania* Parasites.** *Ann. Biochem. & Exper. Med.* Calcutta. 1945, v. 5, No. 3, 95–6.

The author has shown that the flagellates in cultures of leishmania, both in liquid and on solid blood media, are highly resistant to penicillin, though with increase in the concentration of penicillin from 100 to 1,000 units per cc. a decreasing percentage of flagellates survive. Nevertheless, the surviving flagellates in the media containing the highest concentration of penicillin are able to give rich cultures when introduced into penicillin-free media. Advantage is taken of this resistance to penicillin in the isolation of *Leishmania tropica* from contaminated skin lesions. The contaminated material from the lesion is inoculated into liquid or solid medium containing penicillin (200 to 1,000 units per cc.). After a few days' incubation at 22°C., subculture into penicillin-free medium is made, or if staphylococci are still present, once more in a penicillin medium. *C. M. Wenyon.*

DOSTROVSKY, A. & SAGHER, F. **Generalized Recurrence in Leishmaniasis (Oriental Sore) : Report of a Case with 110 Lesions.** *Ann. Trop. Med. & Parasit.* 1945, Oct. 10, v. 39, No. 2, 98–100, 4 figs. on 1 pl.

The case described is that of a girl of 10 years of age from Aleppo, who suffered from multiple skin lesions due to leishmania infection. These lesions healed in four months, but about four months later, fresh lesions began to develop at the original foci, and continued to do so till complete relapse of the original condition had occurred. In the course of time certain lesions showed a tendency to spread to new foci by way of the lymphatics. When the patient was seen by the authors after the disease had persisted for four years, there were 110 lesions, some of the larger of which were due to confluence of a number of smaller ones. The distribution was on the face and limbs, including the gluteal region. Some were present also on the inner mucous surface of the lower lip. The lesions were of a lupoid, serpiginous, gummatous and ulcerative type. The diagnosis was established by the discovery of leishmania in smears, and by culture from the lesions. The author concludes that in this case there had been a complete breakdown of the usual cutaneous immunity. As a rule, in the few cases which relapse, this is a local phenomenon involving only one or two of the many healed foci of infection. *C. M. Wenyon.*

PESSÔA, S. B. & BARRETTO, M. P. Contribuição para o estudo da imunidade da leishmaniose tegumentar americana. [**Immunity in S. American Cutaneous Leishmaniasis.**] Reprinted from *1 Reunião Anual dos Dérmato-Sifilógrafos Brasileiros, Rio de Janeiro, 26–28 Sept., 1944.* 1945, 137–51. [26 refs.]

In discussing immunity in S. American cutaneous leishmaniasis, the authors show that, after recovery, the majority of infected individuals possess a solid immunity. Apart from the fact that, as a rule, secondary or relapse lesions do not develop, this is supported by the negative Montenegro reaction and the failure to produce infection by inoculation of living cultures in recovered individuals. In some persons, however, at various times after healing of the primary sore, secondary lesions appear on the skin or mucosae. These are the result of metastatic distribution of parasites, which, in certain cases, have been shown to survive even in the cicatrized lesions. Occasionally there exists a natural immunity, as shown by one or two individuals of a family who alone

fail to acquire the disease though they are as heavily exposed to infection, for many years, as other members who became infected. In some a very mild type develops, illustrating a partial natural immunity.

Experiments on monkeys show that 100 per cent. become infected from inoculation of living cultures. Vaccination of six monkeys with a vaccine of killed flagellates protected four against infection with subsequently inoculated living flagellates. When these experiments were extended to human beings, of 444 vaccinated individuals, 12 (2·7 per cent.) subsequently acquired the disease in an endemic focus, while of 683 unvaccinated individuals, 108 (15·6 per cent.) became infected in the same period. In the vaccinated individuals who were immune, the Montenegro reaction was negative, as in the case of persons who were immune after recovery from the naturally acquired disease. It is concluded that vaccination can play an important part in the prophylaxis of American cutaneous leishmaniasis. *C. M. Wenyon.*

FEVERS OF THE TYPHUS GROUP.

ANIGSTEIN, L. **Problems of Nomenclature of certain Pathogenic Rickettsiae and Rickettsial Diseases.** *Texas Reports on Biol. & Med.* 1946, v. 4, No. 2, 111–18. [12 refs.]

The author stresses the need for an agreed nomenclature of the pathogenic rickettsiae, and of the diseases caused by them. He mentions some of the attempts that have been made to formulate a satisfactory nomenclature, and makes a proposal that a technical "Inter-American" committee should be set up to make recommendations on the subject in accordance with the accepted international rules of botanical nomenclature. He rightly lays emphasis on the importance of simplicity and usefulness in connexion with the choice of names. He admits that the knowledge of the biological properties of the rickettsiae is incomplete and that no final judgment can yet be passed on the exact position of the pathogenic rickettsiae in the system of microbiology. He states that only one of the many names applied to these organisms has received universal acceptance, *viz. Rickettsia prowazeki* Rocha Lima, 1916. He favours the use of the following names: Louse-borne typhus fever; flea-borne typhus fever; Rocky Mountain spotted fever; *Dermacentroxenus rickettsi* Wolbach, 1919; tsutsugamushi disease; and *Rickettsia tsutsugamushi* Hayashi, 1920, but does not express a dogmatic opinion regarding the most suitable names for the organisms causing flea-borne typhus and boutonneuse fever.

[A generally accepted nomenclature for the fevers of the typhus group and their causative organisms is badly needed, but a committee attempting to deal with the matter would encounter a serious difficulty at the very outset. A primary requirement of scientific nomenclature is that each name must apply to something that can be clearly identified and differentiated from all other objects or conditions. Seeing that pronounced differences of opinion still exist among experts with regard to the relationships of the different fevers of the typhus group, it seems necessary to fall back on provisional names, which

ought to convey helpful suggestions of the chief features of the diseases in so far as these are known at the present time.

Two of the names considered most suitable by the author—louse-borne typhus and flea-borne typhus—comply with these requirements, and there seems to be no valid objection to the extension of the same type of nomenclature to the mite-borne and tick-borne fevers of the group. Clinically and pathologically, these diseases are generally agreed to be closely related to classical typhus, and their association with mites and ticks is universally recognized.

Some workers believe that there are two or more tick-borne typhus fevers, so it would be desirable to add the name of the locality of occurrence or of the type of the disease (Rocky Mountain, boutonneuse, etc.).

Each of the causative organisms of the different typhus fevers could be referred to as the rickettsia of the fever concerned.

The use of this system of nomenclature would not imply adhesion to one or other of the conflicting views regarding the antigenic relationships of the causative organisms. The name " typhus fever of unknown or doubtful vector " would cover the cases in which no satisfactory evidence can be obtained to incriminate any one vector, and in such cases the addition of the name of the serological type (*OX19*, *OXK*, *OX2*, or " indeterminate ") would be helpful.

In the interests of brevity the word " borne " could be dropped without fear of causing misunderstanding.

The rules of botanical nomenclature are not applicable to the names of diseases, and the time is not ripe for a final pronouncement on the names of he rickettsiae of the typhus fevers.] *John W. D. Megaw.*

Macchiavello, A., Cifuentes T., O. & Ovalle, H. Estudios sobre tifo exantematico. V. Influencia de la administración parenteral de altas dosis de acido ascórbico en la evolución del tifo Europeo (no orquítico) experimental del cobayo. [**The Effect of Parenteral Administration of Large Doses of Ascorbic Acid on the Evolution of Experimental European (Non-Orchitic) Typhus in Guineapigs.**] *Rev. Chilena de Hig. y Med. Preventiva.* 1945, Sept., v. 7, No. 3, 175–87, 1 fig. [11 refs.] English summary.

The authors report the results of experiments designed to show whether large doses of vitamin C have a preventive or curative action in guineapigs infected with typhus rickettsiae.

Ten guineapigs were given daily doses of ascorbic acid ranging from 50 to 1,000 mgm. by subcutaneous or intramuscular injection, starting from the day on which they were inoculated with epidemic-typhus rickettsiae. These animals, and 15 controls infected in the same way, were given the usual vegetable diet. The effects observed are described in detail; they can be summarized as follows:—(1) pronounced, but temporary, antipyretic action proportional to the doses given; (2) diminution in the number of brain nodules; (3) a toxic action, shown by hypothermia, or even death; (4) an absence of anti-rickettsial action, as shown by the normal duration of the incubation period, the return of the fever curve to the usual type after cessation of the injections, and the retention of the viability and virulence of the infecting rickettsiae.

It is also pointed out that in Chile the morbidity of typhus fever is highest during the spring and summer when the diet of the people is richest in vitamin C. *John W. D. Megaw.*

Macchiavello, A., Cifuentes, O. & Ovalle, H. Estudios sobre tifo exantematico. VI. Influencia de la vitamina C sobre la evolución de la curva en el tifo exantemático humano y experimental del cobayo. [**The Effect of Vitamin C on the Fever Curve of Exanthematic Typhus in Man and Experimental Guineapigs.**] *Rev. Chilena de Hig. y Med. Preventiva.* 1945, Sept., v. 7, No. 3, 189–96, 1 fig. English summary.

Eight guineapigs were given daily subcutaneous injections of ascorbic acid in doses of 100 to 1,000 mgm., starting from the first day of fever resulting from inoculation with epidemic-typhus rickettsiae. The effects were similar to those described in the preceding paper except that the typhus nodules were more abundant. The two guineapigs that received doses of 1,000 mgm. died after two and six days, and no cause of death other than the toxic action of the drug could be detected.

Intravenous injections of ascorbic acid were given to 23 epidemic-typhus patients in daily doses of 100 to 600 mgm. The average response was a fall of the temperature by 0·5 to 1·0°C. In a quarter of the cases, the duration of the fever was reduced to 10–12 days, and in one-third of the patients there was an apparent improvement in the general condition, but there were five deaths, including two in cases in which the treatment had been started on the 3rd and 5th days.

The action of the drug was regarded as being similar to that of any effective antipyretic. In one case rickettsiae were isolated from the patient's blood after the temperature had fallen to normal. *John W. D. Megaw.*

Macchiavello, A. & Ovalle, H. Estudios sobre tifo exantematico. VII. Estudio experimental acerca de la acción *in vitro* del acido ascórbico sobre el virus del tifo exantemático epidémico (Europeo). [**An Experimental Study of the Action in Vitro of Ascorbic Acid on the Rickettsiae of Epidemic Typhus (European).**] *Rev. Chilena de Hig. y Med. Preventiva.* 1945, Sept., v. 7, No. 3, 197–209, 1 fig. English summary.

In a series of controlled experiments various suspensions containing the rickettsiae of epidemic typhus were kept in contact with acid and neutral solutions of ascorbic acid for 5 to 15 minutes at a temperature of 37°C., and then used to inoculate guineapigs. The only inhibiting effects observed were with the acid suspensions, and it was concluded that the acidity of the inoculum was responsible for these, so that there was no evidence of any anti-rickettsial action *in vitro* by vitamin C. Even if there should have been any anti-rickettsial action this must have been transitory and reversible ; it did not affect the viability or virulence of the organisms. For details of the experiments the original paper must be consulted. *John W. D. Megaw.*

Davis, D. E. & Pollard, M. **Prevalence of Typhus Complement-Fixing Antibodies in Human Serum in San Antonio, Tex.** *Pub. Health Rep.* Wash. 1946, June 21, v. 61, No. 25, 928–31.

The authors carried out complement-fixation tests on the sera of 4,219 persons engaged in food-handling in San Antonio, Texas. Wassermann-positive sera were excluded to avoid the possible fallacy due to false positive reactions. The antigen was prepared from the Wilmington strain of murine rickettsiae ; complete fixation with serum diluted 1–10 was regarded as indicating the occurrence at some earlier date of an attack of murine typhus.

The percentages of positive reactions in the various groups of persons tested are shown in the table.

	Number tested	Percentage found positive
Whites—Male	562	2·3
Female	1,065	3·0
Latin-American—Male	920	5·0
Female	1,340	3·2
Negroes—Male...	114	4·3
Female	218	4·1
Total	4,219	3·5

Although the authors admit that the persons tested were specially exposed to risk because of their occupation, the results are regarded as showing that many cases of murine typhus had not been reported, presumably because they were sub-clinical. *John W. D. Megaw.*

McCulloch, R. N. **Studies in the Control of Scrub Typhus.** *Med. J. Australia.* 1946, May 25, v. 1, No. 21, 717–38, 14 figs. [Numerous refs.]

This paper consists for the most part of a report on the introduction and practical application of dibutyl phthalate as a method of controlling scrub typhus among the Australian troops in the recent war. At the end of 1942, information was received from the U.S.A. that dimethyl phthalate was of special value in protecting against the bites of larval mites when applied to half-inch bands to "all entrances to clothing," and to wider bands on the socks. The author, who was appointed to study the methods, started work at Sydney in March 1943, and continued his investigations in South Australia, Queensland, New Guinea, and Borneo.

In early experiments it was found when dimethyl phthalate was rubbed on the clothing, using 1·0 to 1·25 cc. for each square foot, bites were prevented for two days, but that application in bands four inches wide, using 3·5 cc. per square foot, to all entrances to the clothing failed to give protection against bites. The chemical appeared to act by poisoning rather than by repelling the mites, which travelled freely on the treated clothing but died after about an hour's contact.

Dibutyl phthalate was found by test to be even more effective, and as it could be made available in larger quantities it was used in the further tests. DDT had also been tested, but sets of clothing treated by sprinkling with four ounces of petrol or six ounces of kerosene containing 5·0 gm. in solution, or by dusting with 7·5 gm. of the powder, ceased to be protective after the clothes had been washed four times in soap and running water, whereas one ounce of dibutyl phthalate rubbed into the clothing remained protective after eight washings in the same way.

The efficacy of various methods of treating cloth was tested by applying the larval mites to squares of the treated fabric, mounted on three-ply boards, and finding the time that elapsed before the mites ceased to move. Full details are given of numerous experiments. In New Guinea it was found that when larvae of *Schöngastia blestowei* or *S. pusilla* were applied to cloth treated with

dibutyl phthalate at a rate corresponding to one ounce for each set of field clothing, all movement was arrested within a maximum period of about half an hour, even after the cloth had been washed up to eight times with soap and running water, in the manner available to troops in the field. The results were equally satisfactory whether the application was made by hand rubbing, or by sprinkling with emulsions, or with mixtures of the chemical and alcohol. Laundry washing, involving two periods of washing for ten minutes with soap solution at 135°F., and three machine rinsings totalling 15 minutes, caused an appreciable diminution in the toxic effect so that clothing washed twice in this way was no longer protective. These tests were made with cotton clothing; woollen cloth treated in the same way ceased to be protective after three to seven washings in soap and running water when vigorous rubbing formed part of the procedure, but when the orthodox method of squeezing was employed, the protective effect persisted as well as it did in the case of cotton cloth.

In the numerous conditions in which the tests were carried out, there was no evidence of a breakdown in the protection afforded, except in the case of woollen socks, for which more frequent treatments were found desirable.

In some of the tests a few larvae of *Schöngastia parva*, *Trombicula minor*, *T. fletcheri* (now regarded as a synonym of *T. akamushi*), and *T. hatorii* were included; all of these seemed to be fully susceptible, but some species of *Guntherana* and *Acomatacarus* remained active twice as long.

In tests carried out in Queensland, *T. minor* was found capable of prolonged survival, on treated fabrics, after four or five washings.

The standard method of treating service clothing in field conditions was to supply each man with one ounce of dibutyl phthalate for each set of clothing. The fluid was poured into an open tin; a little at a time was taken up by the finger tips of one hand, spread over the palmar surfaces of both hands, and smeared on the clothing. About 75 applications of this kind could be made from one ounce, in such a way as to make a light, uniform, smear over the shirt, trousers and socks. Fortnightly treatments were regarded as affording reliable protection even in severe conditions of wetting with rain and sweat, and the protection persisted after washing six or seven times with soap and water. Treated clothing, if stored unused and without washing, remained fully protective for at least two months.

The fluid was not irritating to the skin, except over the scrotum, even when applied directly, but when it was used as a mosquito repellent, great care had to be taken to prevent entry into the eyes.

In some cases it was found advisable to treat the socks once a week. Blankets were treated in the same way once every six months, one ounce and a-half was enough for each article.

Benzyl benzoate, stated in U.S.A. confidential reports to be an outstanding miticide when applied to clothing, was not available for testing. Dimethyl phthalate, though more rapidly toxic than dimethyl phthalate to larval mites when applied to clothing not afterwards washed, ceased to be protective after one to three washings. Two American mosquito repellents, "Staway" and "Rutgers 612" were found highly protective, but ceased to be effective after washing.

Statistics are given to show the striking reduction in the incidence of scrub typhus that resulted from the systematic adoption of the treatment of clothing. In cases of apparent failure it was almost always found that the substance had not been properly applied. Almost complete control of scrub itch was also obtained.

Some notes are given on the habits of larval mites. The most rapid rate of travel on cloth was about 1 in. in four seconds. Boot collecting, though

tedious, was a valuable method of obtaining information regarding the prevalence of mites, and a search for infestation of the local animals was regarded as being essential. No complete explanation could be found of the remarkable manner in which the larvae detected the presence of their potential hosts; earth movement was one factor, but not the only one. When an article like a spectacle case was placed on the ground, *T. minor* would promptly crowd on it; when the owner moved away the larvae soon departed, but on his return they again crowded on it.

The known vectors of scrub typhus, *T. deliensis* (syn. *T. walchi*) and *T. akamushi* (syn. *T. fletcheri*) were scarce in boot collections; both were slow-moving and late in appearing, but they were found in nearly all the New Guinea areas visited by the author, mostly in kunai grass, but sometimes also in the jungle; they were numerous on some rats.

Altogether 45 species of mites were found in the course of the investigations, including nine species described as new by WOMERSLEY, and 12 not yet fully studied. Brief notes are given on the more important species.

Entomologists will find much to interest them in the paper.

John W. D. Megaw.

BRODY, J. **A Case of Tick Typhus in North Queensland.** *Med. J. Australia.* 1946, Apr. 13, v. 1, No. 15, 511–12.

A case is briefly described in which the clinical course and Weil-Felix response suggested the diagnosis of tick-borne typhus.

The patient, a female aged 50 years, had lived in a "secondary-scrub area" for eight weeks before the onset of the fever. There was no history of a bite by a tick. The attack lasted 12 days; the onset was with chills and headache; the fever was remittent; and the patient was not seriously ill.

A papular rash was observed on the trunk and limbs; it did not extend to the hands or face; the spots were dark red, about 5 mm. in diameter and raised about 0·5 mm. above the skin level; they were still faintly visible 17 days after the onset. No eschar was found, and there were no complications.

The agglutination titres on the 7th, 14th and 21st days respectively were:— with *Proteus OX2*, 1–160, 1–640, and 1–1,280; with *Pr. OX19* they were 0, 1–80, and 1–160, on the corresponding days. The reaction with *Pr. OXK* was presumably negative because it is stated that the findings were "in marked contrast with those observed in scrub typhus in which the serum agglutinated this organism to a significant titre." CILENTO is quoted as stating (1940) that no fever of the tick-typhus group is known to occur in Australia.

John W. D. Megaw.

ANIGSTEIN, L. & BADER, M. N. **Anti-Rickettsial Activity of Para-Aminobenzoic Acid (PABA): Effect of PABA on Experimental Spotted Fever.** *Texas Reports on Biol. & Med.* 1946, v. 4, No. 2, 260–78, 5 charts. [16 refs.]

In a series of fully-controlled experiments the authors found that when 2·0 gm. PABA was added daily to the food of guineapigs, starting on the day of inoculation with a virulent strain of Rocky Mountain spotted fever rickettsiae, clinical manifestations of infection failed to appear in about 80 per cent. of the animals; in the remaining 20 per cent. there was abortive fever, but the total recovery rate was almost 100 per cent., whereas none of the untreated controls survived.

Delayed treatment was given to four lots, each of four inoculated guineapigs. With one lot the drug was started 24 hours after inoculation; one of the four

animals died and another had an abortive attack. When the delay was 48 hours, two of four animals died ; when it was 72 hours, all but one died, and when the treatment was delayed until immediately after the onset of the fever, there was no survival.

The drug was given to six guineapigs for five consecutive days and then the animals were inoculated ; all of them died.

Guineapigs that recovered after treatment were found to have enlarged and friable spleens, from which rickettsiae could be recovered. Complete immunity was found to have been established, so that the animals must have suffered from sub-clinical attacks, and it appeared that the drug had acted " by stopping the further multiplication of the parasites rather than by killing them outright."

John W. D. Megaw.

DENGUE AND ALLIED FEVERS.

SANDLER, A. **The Clinical Picture of Papataci Fever, especially in Palestine.** *Med. J. Australia.* 1946, June 8, v. 1, No. 23, 789–96.

The author describes the features of sandfly fever as observed in 210 cases among Jewish students in Jerusalem during the years 1935–1942. Some of the signs and symptoms regarded as characteristic by certain authors were missing. No attack lasted longer than four days ; there was no catarrh of the upper respiratory passages, no swelling of the glands and no rash in any case. Brief diarrhoea occurred in six cases, but this condition was prevalent in Jerusalem at the time and may not have been associated with the disease. Pain localized in the eyeballs was not a special feature, and pronounced conjunctivitis never occurred. There were recurrences in seven cases ; after three days in five, after nine days in one, and after five weeks in the remaining case, in which it was probably a reinfection. In two cases a second attack occurred within a year. Severe pains in the thighs were pronounced features of almost all the cases in two epidemics during the period 1935–1937. Recovery was " smooth and rapid."

The author mentions that the word *papataci* is Italian and means " secret biter " [Hoare's Short Italian Dictionary gives the word *pappataci* as meaning " husband who shuts his eyes to his wife's goings on."].

Most of the paper consists of a detailed discussion of the discrepancies occurring in the descriptions of the disease by various writers, and the natural conclusion is reached that there are " considerable variations in the symptomatology of papataci fever." It is believed that there are three or four different forms, any of which may occur in the same country.

[The chief interest of this paper lies in the documentary evidence collected to show the great variability in the manifestations of the disease. The author inclines to the view that the symptomatology is uniform in each outbreak, though he admits that he has excluded a number of cases, chiefly because of the absence of thigh pains, which " were possibly of papataci fever."

John W. D. Megaw.

PLAGUE.

DAVIS, D. H. S. **Plague in Ngamiland, Bechuanaland Protectorate.** *Union of South Africa Ann. Rep. Dept. Public Health Year ended 30th June, 1945*, 51–2.

In this abbreviated report on the survey of Ngamiland many interesting points of plague epidemiology are raised and illustrated. As an epidemic of plague it was the " largest outbreak in Southern Africa on record " and furnished 304 total cases, with 156 deaths ; the true mortality, however, was probably nearer 60 than 50 per cent. It began with the notification " in the first week of October, 1944 " of a number of sudden deaths in a population of 15,000 persons. Recognition of the nature of the disease was soon forthcoming and measures were hurriedly adopted to deal with prevention of spread. These were :— anti-plague vaccination [presumably with a killed vaccine] ; recruitment of an anti-rodent staff to engage in hut-spraying, application of cyanogas, and destruction of vermin ; quarantine of areas concerned and prohibition of inter-kraal movement. Most of the cases were bubonic, but some, invariably fatal, were septicaemic or pneumonic. There was no doubt that the insect vectors were plague-infected fleas, and most of these were " without rodent hosts for much of the epidemic " ; this fact has special significance in view of the data which are now accumulating on the survival time and transmission potentiality of the plague flea. Moreover, this epidemic has the added interest of showing the connexion not only of epidemic with epizootic, but also of epidemic with sylvatic plague. The rodent concerned, the multimammate mouse, belongs to the class of the semi-domestic mice. There was an unusually favourable season for increase in the population of these small rodents, which synchronized with the peak of a secondary plague epizootic in them (from a primary epizootic in gerbils) and with flooding of swamp rodent burrows. The consequent overcrowding of the mice, and food shortage, sent the rodent population to the human habitations, the villages and kraals, to get grain and other food. " With the onset of warmer weather in September and October climatic conditions for the spread of plague from infected rodent fleas to man became more favourable and the human epidemic resulted." A series of recommendations, applicable to " the primitively housed population of Ngamiland," are given, and special note is made of the great possibilities of DDT " for the control of insect-borne diseases " in such a population. *W. F. Harvey.*

BLANC, G. & BALTAZARD, M. Virulence des déjections de puces pesteuses. [**Virulence of Plague-Flea Dejecta.**] *Ann. Inst. Pasteur.* 1946, May–June, v. 72, Nos. 5/6, 486–9, 1 fig.

Originally, several thousand fleas were fed on plague-infected guineapigs, and once these fleas were definitely infected they were placed in a flea-house to which only fresh fleas were afterwards added. These fresh fleas usually became infected by the second day. Breeding took place, and litters of new fleas became infected on the animals contaminated by their predecessors. The process had gone on for 1½ years when flea dejecta were removed, for the purpose of these experiments, from the hair of a white rat which had been placed in the flea-house ; this rat was dead by the following evening, of proved plague. The dejecta were sealed in an ampoule, and kept in the dark at room temperature. Tests of this material by subcutaneous inoculation of guineapigs proved that it was still capable of causing plague after 24 hours, 122 days, 190 days, 316 days 1 year, and 16 months. The significance of these experiments is obvious. It would seem probable that the virulence of dejecta in burrows can be long maintained

and that this would suffice to provide one explanation of the endemicity of plague in rodents. Still further deductions are permissible which would extend infectivity, *via* the faeces, not only to the human flea but also to the louse, especially as it has been shown that mice can be infected through mucous membranes by dejecta of *Pulex irritans* from human plague habitations.

W. F. Harvey.

AMOEBIASIS AND INTESTINAL PROTOZOAL INFECTIONS.

WATSON, J. M. **The Effect of Urine on** *Entamoeba histolytica*. *Ann. Trop. Med. & Parasit.* 1945, Oct. 10, v. 39, No. 2, 101–16, 1 fig. [31 refs.]

The author has investigated the action of urine on *E. histolytica* from the point of view of the possibilities of urinary amoebiasis. He has shown that at the temperature of the human body, urine is highly lethal to the amoebae, which are quite unable to live in it. The lethal effect, however, develops slowly, the first signs being noticeable in two hours. Exposure to urine of various concentrations, either alone or mixed with faeces, at lower temperatures for periods exceeding two or three hours, results in a gradual reduction in the numbers of amoebae and loss of motility in those that remain. After 24 hours the majority of the amoebae are degenerate and quite unrecognizable. These results emphasize anew the well-known rule that in the collection of faecal samples for diagnosis of amoebic infection, it is imperative to avoid admixture with urine. Tests were carried out in order to discover the cause of this lethal action. The amoebae were shown to be capable of surviving and multiplying in media with a *p*H as low as 5·9, while they remain uninjured by still lower *p*H values for several hours. As regards osmotic pressure, the amoebae can live in solutions equivalent to Ringer's solution of from 0·3 to 1·7 times the normal strength. Quite apart from the lethal action of variations in *p*H or osmotic pressure, urine may be toxic on account of two of its constituents, namely urea and ammonia, both of which killed and disintegrated all amoebae in culture tubes in 48 hours.

From the results of his experiments the author concludes that it must be extremely difficult for *E. histolytica* to establish itself in any part of the urinary tract where it will be continuously immersed in urine. On the other hand, amoebic invasion of the walls of the urinary passages by direct or metastatic extension might occur in such a manner that the amoebae in the wall were not continuously bathed in urine. From such lesions amoebae might from time to time escape into the urinary passages, and if rapidly voided before degeneration occurred, give rise to a diagnosis of urinary amoebiasis. Actually, however, there is no information available regarding the condition of the walls of the urinary passages in the few cases of urinary amoebiasis which appear to be authenticated. [See also the critical review of urinary amoebiasis by the same author, this *Bulletin*, 1945, v. 42, 947.] *C. M. Wenyon.*

SNELL, A. M. **Some Clinical Problems of Amebiasis.** *U.S. Nav. Med. Bull.* 1946, July, v. 46, No. 7, 1023–40, 2 figs. [18 refs.]

The author has written this paper in view of the increased occurrence of amoebiasis in the United States as a result of the return there of men infected overseas. Whilst it contains nothing original, the paper consists for the most part of a well-balanced appreciation of the epidemiology, pathology, clinical picture, complications and sequelae, diagnosis and treatment

of amoebiasis. The fundamental diagnosis of the condition by finding the parasite is suitably stressed, and the need for tenacity of purpose and for skill in the procedure is mentioned; the ancillary methods of examination are discussed in proper perspective. The remainder of the paper contains brief accounts of four cases of amoebiasis illustrative either of its main features, or of the difficulties in its diagnosis when associated with complicating diseases.

[In the reviewer's opinion this paper is an admirable and up-to-date general account of amoebiasis worthy of wide circulation.] *A. R. D. Adams.*

Proc. Roy. Soc. Med. 1946, July, v. 39, No. 9, 541–50 (Sect. of Proctology 9–18). **Discussion on the Use of Medicaments in Diseases of the Colon and Rectum.** [Murgatroyd, F.; Hargreaves, W. H.; Lovibond, J. L.; Somervell, T. H.; Morgan, C. N.; Wright, A. D.; Hunt, A. H.]

Opening the discussion, Murgatroyd stated that the drugs commonly used in the treatment of amoebiasis fall into three groups:—(1) Ipecacuanha derivatives (emetine hydrochloride and emetine-bismuth-iodide); (2) substituted phenyl arsonates (carbarsone and stovarsol); and (3) iodoxyquinoline compounds (chiniofon and diodoquin). After brief consideration of the treatments in vogue for amoebiasis, he stated that the successes achieved had been variously assessed as between 75 and 95 per cent. To understand the failures it is necessary to consider the parasite, the patient and the procedure. There is no sound experimental evidence that drug resistance is acquired by the parasite. Whether some amoebae live in the bowel as commensals, or whether all live in the tissues, has not been established. The state and distribution of the drugs in the body is a matter of speculation; in the cat, emetine, given parenterally, is largely excreted in the urine, and fails to cure an *E. histolytica* gut infection; in man it fails to sterilize most of the acute cases, and it is particularly poor in this respect in chronic carriers. Emetine given to man by the mouth is much more effective in producing cure, and this may be due to its slower absorption by this route and the consequently longer maintenance of an amoebicidal concentration in the tissues. The control of a concomitant bacterial colitis may render an amoebic infection more amenable to successful treatment, but the primary aim should be to sterilize the amoebic infection before such a condition develops.

Hargreaves spoke of the chronic bed-ridden cases of amoebiasis from Burma seen by him after they had received many emetine injections and other treatments, both overseas and at home. He found the outlook for these distressing cases considerably changed when penicillin was given, as it rendered the amoebic dysentery more amenable to specific drugs. Its use, with sulphasuxidine concurrently, was therefore adopted for such cases, as a preliminary to a combined course of anti-amoebic treatment. Penicillin and sulphasuxidine treatment was tried for chronic ulcerative colitis in nine cases, with satisfactory immediate results, although permanent cures could not be claimed.

Lovibond reviewed his clinical impressions of about 1,000 hospital cases of amoebic dysentery in Ceylon, Assam and Burma, and concluded that a continuous sequence of treatment is all-important. E.B.I. and chiniofon enemata are possibly the keystones of treatment, and " Carbarsone should clear residual cysts."

Howard Somervell, recording his South Indian experience of colonic disease, said of amoebiasis that most of the work of the medical wards seemed to be " clearing up the failures of other doctors by giving continuous courses

of emetine to patients who had already had scores of injections, but never more than five or six at one time." He stressed the importance of continuous daily treatment with E.B.I. for at least 12 days, and the need for adjuvant treatment with quinoxyl retention enemata in chronic cases. He referred to 10 cases of amoebic disease of the rectum, and four of amoebic abscess in the perineum and buttocks, in which surgery and emetine treatment were effective. All cases of carcinoma of the rectum in the tropics should be examined for amoebae before operation or radium treatment. He related his experience with cases of concurrent bacillary and amoebic dysentery, of bacillary dysentery, and of tuberculous disease of the colon.

Naunton MORGAN spoke of the difficulties in differential diagnosis of amoebic tumours of the gut, and the dangers of operation in undiagnosed amoebiasis or bacillary infection. In discussing the use of sulphasuxidine in the surgery of the rectum and colon, he recommended bigger dosages prior to bowel surgery than those originally advocated by POTH.

Dickson WRIGHT listed a number of conditions, including amoebic dysentery, which benefit from "sterilization of the faeces" by suitable sulphonamide therapy; and HUNT recorded data showing the reduction in the incidence of peritonitis complicating major intraperitoneal surgery of the colon and rectum after pre-operative sulphasuxidine treatment. *A. R. D. Adams.*

RADNA, R. Sur le traitement de l'amibiase par l'iodoforme. (Deuxième note.) [**The Treatment of Amoebiasis with Iodoform.**] *Ann. Soc. Belge de Méd. Trop.* 1945, Dec. 31, v. 25, No. 3/4, 219–20.

The author treated 18 carriers of cysts of *E. histolytica* with iodoform, using the technique recommended by CASTELLANI and SCOTTI. The iodoform was given in small gelatin capsules, each contained in a much larger capsule of sodium bicarbonate.

Each capsule of iodoform contained 0·05 gm. One such capsule was given on the first day of treatment, two on the second, four on the third and six on the fourth day. The dose of six capsules was continued until the fourteenth day. A second course was given after a month's rest. For the two courses, a total dosage of 7·3 gm. was thus administered. Twelve of the patients were free from cysts after 15 days of treatment, and 16 after 1 month.

The author points out that the relatively low price of iodoform makes it possible to employ it on a large scale in the sterilization of carriers of *E. histolytica* cysts. *H. J. O'D. Burke-Gaffney.*

BRUG, S. L. **Pseudoparasitism of the Human Intestinal Tract.** *J. Parasitology.* 1946, June, v. 32, No. 3, 222–4, 1 fig. [14 refs.]

"On one day, in four out of thirteen fecal samples from a psychiatric ward, coccidial oöcysts, probably of *Eimeria deblieckí*, were found. The cysts stained red with eosine solution, and were apparently dead. Possibly they had been ingested with liver sausage for the preparation of which pigs' bowels may have been used."

RELAPSING FEVER AND OTHER SPIROCHAETOSES.

D'IGNAZIO, C. & CODELEONCINI, E. La forma polmonitica della febbre ricorrente e la polmonite primitiva dermotifosa. Nota clinica. [**Pneumonic Form of Relapsing Fever and of Typhus.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1945, v. 5, Nos. 5/6, 211–20. English summary (3 lines).

Details are given of four cases selected from a larger number. They are important to note because in all of them the symptoms pointed strongly to a lobar pneumonia of the ordinary pneumococcal type—pain, cough, fever, haemorrhagic sputum and signs of consolidation—but the basic disease was relapsing fever or typhus. Eighteen of the former are mentioned and 12 of the latter. The four detailed were sent to hospital as cases of frank pneumonia and it was the presence of an enlarged liver or spleen, and the failure of sulphonamide drugs to relieve which led to further laboratory examination and the finding of the spirochaete in the one type and of a positive Weil-Felix in high dilution (up to 1 : 2,560) in the other. *H. Harold Scott.*

D'IGNAZIO, C. Schemi di terapia delle febbri ricorrenti africane. [**The Treatment of African Relapsing Fever.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1945, v. 5, Nos. 5/6, 17–27. English summary (2 lines).

The author gives his views on the treatment of relapsing fever in Addis Ababa, which is chiefly louse-borne. He uses neosalvarsan, bismuth and stovarsol. [The author refers to "neosalvarsan" and "salvarsan" indiscriminately.] In the early febrile stage he gives neosalvarsan in fairly large doses (0·6–0·75 gm.) intravenously with, or without, Hepatamin [presumably a liver preparation] as a "protective", and injected slowly. In the second attack of fever, to forestall renal and hepatic lesions, he gives first a small dose of 0·1 or 0·15 gm. neosalvarsan, to test the patient's tolerance, and then returns to the larger dose (0·6 gm.). After the crisis there may be no more attacks, but as a prophylactic 0·3 gm. may be given intravenously and repeated "every 3–4 days for 3–4 times." When the patient has had 1·8–2·1 gm. in the fortnight after the attack, and there has been no relapse, he may be regarded as cured. The author is not an advocate of the still larger doses (0·9 gm.) as recommended by some physicians.

For treatment during the afebrile period the following course is favoured: If begun during the first three days of calm, injections of neosalvarsan should be made intramuscularly on alternate days in doses of 0·2, 0·3, 0·4, 0·5, 0·6 and 0·6 gm., the interval between the penultimate and the last dose being 3 days. If administered in the second three days, in view of the early return of fever, a larger initial dose is given, 0·4 gm., repeating it twice on alternate days, then 0·5 gm. "repeating thrice" [totalling, says the author, 2·1 gm. but, as stated, the total would be 3·2 gm. He is presumably referring to neosalvarsan, in view of the relatively high dose].

Bismuth he uses in doses of 30–40 cgm. suspended in oil and injected intramuscularly. If desired, it may be given on the days intervening between those for injection of neosalvarsan.

Stovarsol *per os* is useful for children. To the very young he gives 0·25–0·45 gm. daily for 10 or more days. For children "in the second infancy" [? 5–10 years] the dose is 0·5–0·7 gm. daily for the same length of time. For adults during the fever period he gives 1·25–1·5 gm. on two consecutive days, and he has obtained cure without further treatment. During the afebrile period he gives 0·75 gm. daily for 7–8 days and claims that he has usually obtained a cure by this means; in exceptional cases a longer course is needed.

Patients presenting signs of hepatic inadequacy—jaundice, epistaxis, petechiae, with pain over the liver—are given 50–80 gm. of glucose daily and 10–20 units of insulin subcutaneously. If the glucose causes vomiting when taken by mouth it may be given intravenously in 10 per cent. solution, 10–20 cc. at a time. For headache the ordinary antineuralgics usually suffice, but if it is very severe lumbar puncture may be needed [the quantity of fluid to be withdrawn is not stated]; for the rheumatic symptoms "salicylates may be given by mouth, by rectum or by injection, and vitamin B intramuscularly or intravenously." *H. Harold Scott.*

YAWS.

DWINDELLE, J. H., REIN, C. R., STERNBERG, T. H. & SHELDON, A. J. **Preliminary Report on the Evaluation of Penicillin in the Treatment of Yaws.** *Amer. J. Trop. Med.* 1946, May, v. 26, No. 3, 311–18, 1 graph. [10 refs.]

The authors review seven papers on the subject and find that although clinical cure of yaws has resulted even with small doses of penicillin (50,000 to 500,000 Oxford Units), very few cases were observed to attain Kahn or Wassermann "sero-negativity".

The present work was done in a part of Haiti where syphilis was not prevalent. Three groups of patients were studied; the details are set out in the Table below.

Approximately 60 per cent. in each series were under 17 years of age. The diagnosis of yaws depended on clinical and serological findings. In a check group of 26 patients in Series A, spirochaetes were demonstrated on dark field examination in all cases. Considerable efforts were needed to follow cases after treatment. In Series A at 3 months 72 per cent., and at 6 months 84 per cent., and in Series B and C at 3 months 60 and 66 per cent., respectively, were re-examined. Observations in all series are to continue for one year.

In Series A, skin lesions began to dry in 24 hours, pain in the joints, and plantar and palmar yaws, disappeared in 2–3 days. In most cases healing was complete in one month—a few ulcerated primary lesions with bacterial infections had healed by the second month. In Series B and C all lesions had healed in 3 months except three "ulcerated primaries". [These were probably primary lesions in pre-existing ulcers; in these the ulcers are unaffected by anti-yaws chemotherapy.]

At 6 months in Series A only two cases showed possible plantar lesions, indicating relapse. At 3 months in Series B one case was similarly a possible relapse, and a second might have been re-infected. However, no serological relapse preceded these clinical manifestations.

Only 3 of the 500 cases had negative Kahn reactions before treatment. In Series A at 3 months after treatment, 98 per cent. showed reductions in serological titre, mostly to a quarter of the initial titre. A number of serological tests, including the Quantitative Kahn and Quantitative Kolmer tests, were employed, and were carried out at the Army Medical School, Washington. At the end of 6 months only 17 cases (10 per cent.) in Series A had negative Kahn tests; the others showed further slight reductions in titre. Similar results were observed at 3 months in Series B and C, in which only one case had a negative Kahn test.

Dark field examinations were negative in 8–12 hours after treatment, and biopsy material was negative for spirochaetes after 22 hours.

TABLE 1.

Age distribution of and total amount of penicillin given to primary and secondary yaws patients

Age groups	5 years and under	6–12 years	13–16 years	17 years and over	Total	Vehicle	Method of administration
Series A— Total dosage penicillin in 4 days	13 1,200,000 O.U.	60 1,200,000 O.U.	41 1,200,000 O.U.	86 1,200,000 O.U.	200	Penicillin sodium in aqueous solution	Hospitalized. 30 intramuscular injections of 40,000 O.U. every 3 hours
Series B— Total dosage penicillin in 2 days	0	74 600,000 O.U.	27 900,000 O.U.	50 1,200,000 O.U.	151	Penicillin calcium in peanut oil with 4·8 per cent. beeswax by weight	Ambulatory. Intramuscular injections at intervals of 24 hours
Series C— Total dosage penicillin in 1 day	0	56 600,000 O.U.	35 900,000 O.U.	58 1,200,000 O.U.	149	Same as Series B	Ambulatory. Intramuscular injections at an interval of 10–12 hours
Total number patients	13	190	103	194	500		

No severe toxic reactions were encountered. Half the patients in Series A had a pyrexia (100–104°F.) 2–8 hours after treatment started ; these had subsided in 10–12 hours. One-fifth of the patients had secondary pyrexia on the 3rd–5th days of treatment.

The authors point out that in active early syphilis similar prompt clinical response would have followed the same treatment, but after 6 months 70–80 per cent. [some British figures are higher] would have had negative serological tests. It is unlikely that concomitant malaria or syphilis interfered with the serological tests. From the results in Series A in which children and adults received equal doses, it would appear that doses in excess of an optimum have no proportionate curative effect. The results of observations for 12 months will be reported later. *C. J. Hackett.*

Stubenbord, W. D. **Yaws : Treatment with Penicillin.** *Southern Med. J.* 1946, Aug., v. 39, No. 8, 608–9, 2 figs.

A report of a single case.

HELMINTHIASIS.

Hernández-Morales, F., Oliver-González, J. & Pratt, Caroline K. **The Treatment of Schistosomiasis Mansoni with Urea Stibamine (Squibb). Preliminary Report.** *Amer. J. Trop. Med.* 1946, May, v. 26, No. 3, 327–9

Encouraged by the results of treating human filariasis with pentavalent antimony compounds in intensive doses [Culbertson, Rose and Oliver-Gonzalez, this *Bulletin*, 1946, v. 43, 54 ; 354] the authors have used urea stibamine (Squibb) in the treatment of 14 cases of schistosomiasis due to *S. mansoni*. The cases chosen were those only who were passing large numbers of live schistosome ova. The patients consisted of seven male and seven female Porto Ricans, aged from 12 to 36 years, averaging 26 years for man and 21 for women. Accurate clinical records were kept. Only one-third of the patients showed symptoms referable to schistosomiasis.

Three daily intravenous doses were given, after a small initial dose of 50 to 75 mgm. was given to detect susceptibility. Thereafter, dosage was gradually increased to maximum tolerance.

The amount of the drug tolerated varied from 3·4 gm. to 10·125 gm. The smallest dose was given to a 12-year-old white girl of 73 pounds' weight, who never tolerated more than 150 mgm. ; the largest was received by a 29-year-old white male of 131 pounds' weight. On an average, the men tolerated 7·18 gm. throughout 16 days, and the women 6·69 gm. throughout 13 days.

Toxic reactions were immediate or delayed. The former included flushing, facial oedema, hoarseness, dyspnoea, tachycardia, abdominal pain, nausea, vomiting, conjunctival congestion, and a semi-shock-like condition. Delayed symptoms were generally milder. One death occurred on the 9th day of treatment, in a woman who had received a total of 5·03 gm. of the drug.

In nine cases, white blood corpuscles fell temporarily to about 3,000 per cmm. Four patients showed traces of albumin and casts during treatment.

Stool examinations were made daily before and after treatment. At the end of treatment, 10 patients still showed ova. After one, two, three and four months, 12 patients had completely negative stools. The remaining patient, who only received 3·4 gm. of the drug, was still passing ova 60 days after treatment.

The authors consider that the true evaluation of the drug can only be made after examinations through longer periods of time than the four months recorded ; but they find the results encouraging. *H. J. O'D. Burke-Gaffney.*

Amberson, J. M. **Schistosomiasis and its Control in Egypt.** *U.S. Nav. Med. Bull.* 1946, July, v. 46, No. 7, 977–1010, 7 figs. [13 refs.]

This is a general account of the subject, illustrated by admirable photographs.

Avery, J. L. **The Habitat of the Snail Host of *Schistosoma japonicum* in the Philippines.** *Science.* 1946, July 5, 5.

In 1932, Tubangui [see this *Bulletin*, 1933, v. 30, 210], reported a fresh-water snail, at present designated as *Schistosomophora quadrasi* (Möllendorff) to be the intermediate host of the causative agent of schistosomiasis in the Philippine archipelago.

S. quadrasi has been reported from eastern Leyte, eastern Mindoro, north-eastern Mindanao and Samar. The author's observations relate to southern Samar and around Palo, Leyte, in early 1945. The species is amphibious, but its preference for an aquatic environment is proportional to the temperature. The molluscs were often found as much as four inches above the water surface, on emergent vegetation; but in the hotter parts of the day they migrated beneath the surface, particularly in the shade of trees and shrubs. They were found principally in shallow quiet water, containing much decayed organic matter, particularly coconut fronds. The water usually showed a *p*H of about 6·0. There was often much pollution from human wastes; and in one area 36 per cent. of the *S. quadrasi* examined contained stages of human schistosomes.

Five other species of molluscs were found in the same habitats.

H. J. O'D. Burke-Gaffney.

Nelson, E. C. & Bayliss, M. **Schistosomiasis Japonica—Laboratory Diagnosis.** *Bull. U.S. Army Med. Dept.* 1946, June, v. 5, No. 6, 673–80, 5 figs.

The authors found that direct smear, zinc sulphate floatation and acid-ether extraction techniques were not entirely suitable for diagnosis of eggs of *S. japonicum*, mainly on account of the coated condition of the eggs, which was characteristic of the cases with which they worked. A sedimentation method was therefore devised which proved satisfactory and is designated the *continuous flow funnel sedimentation* technique.

Five to ten grammes of faeces are thoroughly mixed with 100 cc. of tap water, and passed through a 20-mesh screen into the funnel assembly. This consists of a glass funnel with an overflow tube which fits tightly into the funnel outlet and whose upper extremity is a little below the rim of the funnel. Water is run rapidly into the funnel from above, through a fine inlet tube with a bent tip, which is placed at the outer edge and parallel to the side of the funnel at a level slightly below the top of the overflow. When the water is about to overflow the rate of flow is reduced to 100 cc. per 5 minutes. A slow whirlpool is created which carries off fine material through the overflow tube, while the eggs settle at the bottom of the funnel. Ten minutes of this part of the technique is adequate. The overflow tube is then pulled out and the settled sediment released into a urine glass, allowed to settle again, and then examined. [It is to be regretted that the illustration of the apparatus cannot be reproduced satisfactorily in this *Bulletin*.] *J. J. C. Buckley.*

Fishbon, H. M. **A Case in which Eggs of *Schistosoma japonicum* were demonstrated in Multiple Skin Lesions.** *Amer. J. Trop. Med.* 1946, May, v. 26, No. 3, 319–26, 8 figs.

This case relates to a sergeant in the U.S. Army, who was stationed on the island of Leyte in the Philippines for about a fortnight in November/December 1944. He had bathed in a slow-running stream, on the banks of which snails were found.

About a week after his departure, he noted angioneurotic swellings about both eyes, which later involved the whole face. This lasted for three days, and was accompanied by constitutional symptoms ; the fever, which lasted for two weeks, being followed by a dry nocturnal cough persisting for three weeks.

With the cough, there developed grouped pruritic papules on the right subchondral wall, together with a small evanescent group on the right side of the scrotum. The rash extended slowly towards the left abdominal wall, axilla and back, apparently in an intercostal-distribution. The lesions consisted of infiltrative groups of shotty papules.

Early in February, ova of *S. japonicum* were found in the stool. Physical, X-ray and laboratory examinations were otherwise without significance, except for an eosinophilia of 15 per cent.

The author gives a full description of the lesions, which were not vesicular, being herpetiform only in distribution and grouping, which showed a predilection for the 8th intercostal space.

Biopsies of the abdominal wall and back lesions showed inflammatory reactions, which included eosinophiles, surrounding distorted schistosome ova. The latter were better preserved in the specimen from the back, and the contained miracidia were well-stained. Four photographs and two microphotographs illustrate the lesions clearly.

Two courses of Fouadin were given, each consisting of 40 cc. and lasting for a fortnight. The last new skin lesion containing ova with active miracidia was found ten days after completion of the first course. On the last observation of the patient, two weeks after the second course, the skin lesions appeared as small, white, fibrotic papules. The eosinophilia fell to 10 per cent. after the first course and to 9 per cent. after the second. Proctoscopy revealed no schistosome nodules, but the stools remained positive for *S. japonicum* ova throughout.

The authors point out that whilst portal infiltrations by *S. japonicum* have been described, and cases of cerebral and pulmonary involvement have been noted, no adult worms of this species have been described in these vessels in man. The case under review manifests systemic involvement as well. Whilst the author considers the possibility of embolic skin lesions from a distant adult worm, he also believes that such a worm may have been situated in an intercostal vessel. He refers to the case reported by GARCIA *et al.* [this *Bulletin*, 1941, v. 38, 43] in which *S. japonicum* eggs were found in a skin biopsy from a child suffering from a chronic ulcer of the leg. *H. J. O'D. Burke-Gaffney.*

CARROLL, D. G. **Cerebral Involvement in** *Schistosomiasis japonica. Bull. Johns Hopkins Hosp.* 1946, Apr., v. 78, 219. [Summary taken from *J. Amer. Med. Ass.* 1946, July 20, v. 131, No. 12, 1023.]

Carroll reports five cases of cerebral involvement in schistosomiasis japonica which occurred among American officers and soldiers between the ages of 20 and 29 years on the island of Leyte in 1944. In all the cases ova of Schistosoma japonicum were found in the stools ; there was a history of exposure and clinical symptoms and laboratory evidence suggestive of schistosomiasis japonica. Four of the patients presented neurologic involvement in the acute stage of the disease, and one patient showed neurologic involvement four months after the acute stage. Those in the early stage had an acute onset of drowsiness followed by coma and incontinence. There were signs of pyramidal tract involvement with weakness, spasticity and exaggerated deep reflexes. There was moderate eosinophilia. Symptoms improved with therapy. Neurologic involvement in the late stage was manifested by jacksonian convulsions

followed by the development of hemiplegia but without drowsiness, coma or incontinence. The leukocyte count and eosinophil count were normal. There was no improvement with therapy.

CAMERON, T. W. M. **Fish-carried Parasites in Canada. (1) Parasites carried by Fresh-Water Fish.** *Canadian J. Comp. Med.* Gardenvale, Quebec. 1945, Sept., Oct. & Nov., v. 9, Nos. 9, 10 & 11, 245–54 ; 283–6 ; 302–11, 7 figs. [17 refs.]

This is a paper of much interest to veterinarians and to comparative pathologists, written with Professor Cameron's known clarity and succinctness. It will appeal less to human pathologists and physicians because three only of the many species of helminthic parasites referred to infest man, and of one of these only a single case—and that rather doubtful—is on record.

Of the Heterophyidae several species are known to infest domestic cats, dogs, rabbits, white mice and a number of birds. In the Philippines, recently, four different species were found in nine autopsies, and as four of the patients had died from cardiac trouble, it was believed that there was some aetiological connexion between them.

The life-histories of *Anophallus venustus* and *A. brevis* are described in full and diagrammatically depicted. Each has two intermediate hosts ; in the case of *A. venustus* the first is the snail *Goniobasis livescens* ; the cercariae from this attach themselves to the base of the fin of some fresh-water fish (13 are named, among them carp, dace, perch and catfish) shed their tails and penetrate ; the infested fish is eaten by a mammalian or avian host. In the stools of a man in Ste. Anne's Military Hospital, Canada, were found helminth ova " agreeing in appearance with this species."

Another trematode infesting man and also the dog, red fox, mink, raccoon and cat, but not birds, is *Metorchis*. The life-histories of some species of this genus are unknown, but that of *M. conjunctus* is fully described. It is closely similar to that of *Opisthorchis* and *Clonorchis*, with two intermediate hosts, the snail *Amnicola* and a fish, the common sucker (*Catostomum commersoni*). Only in places where the sucker is eaten raw does man become infested.

Clinostomum marginatum occasionally infests man. [Another species has been recorded in man in Japan and is the cause of parasitic laryngopharyngitis, known as *Halzoun* in the Near East. See this *Bulletin*, 1945, v. 42, 396.] The snail intermediate host is *Helisoma trivolvis macrostomum*, " but other related Planorbid snails may also serve as vectors." Its cercaria has a formed tail and encysts on fins or gills or beneath the scales of certain fish, and produces small abscess-like cysts, so that man rarely eats it.

Lastly, there is a *Diphyllobothrium* closely related to the European *D. latum*, but whether the Canadian one is identical with the European is not certain. Its first intermediate hosts are fresh-water crustaceans, *Diaptomus oregonensis*, *D. sicillis* and *D. siciloides*, and the plerocercoids are found in pike and perch. It is one of the commonest cestodes in man in eastern Canada and is found also in dogs often, and in foxes, cats and bears less often. Other tapeworms with fish as intermediate hosts, which may be mentioned, are *Ligua*, *Triaenophorus* and *Proteocephalus*, but these are not infective for man or for domestic animals.

H. Harold Scott.

JORGE, J. M. & RE, P. M. Hidatidosis y procesos graves anafilacticos. [**Hydatid Disease and Severe Anaphylaxis.**] *Rev. Asoc. Med. Argentina.* 1946, June 15, v. 60, No. 583, 445–50. [21 refs.]

PULLAR, E. M. **A Survey of Victorian Canine and Vulpine Parasites. III. Platyhelminthes other than Taenia.**

GELFAND, M. **The Clinical Features of Hookworm Disease.** *Clin. Proc.* Cape Town. 1945, Jan.–Mar., v. 4, No. 1, 21–9.

In this short paper the author discusses some of the still vexed questions of hookworm disease. He points out that the African with hookworm is usually suffering from other parasitic diseases also—malaria, schistosomiasis—or from malnutrition or disorders of the liver ; and that too exclusive a concentration on the diagnosis of hookworm disease, on the evidence of ova in the stool, may be disastrous to a patient. The injudicious administration of an anthelmintic may be fatal in a patient seriously ill from another cause. In dimorphic anaemia (which is the common anaemia of Africa), a cause for the iron loss, such as hookworm, schistosomiasis, malaria or dysentery, can usually be demonstrated ; and it is unlikely that the intake of iron in Africa is unduly low, though the nutritional factor in anaemia is extremely important. Treatment for hookworm infestation alone is therefore usually insufficient to cure anaemia, and, in fact, this mixed anaemia is difficult to treat successfully. In the European the matter is usually very different ; anaemia is slight or absent, but abdominal pain and flatulence are common.

The author has not found that increase in appetite is a marked symptom of hookworm disease, although so often mentioned in text-books ; nor is earth-eating peculiar to those with hookworm, in spite of common opinion. Earth-eating is practised by many African tribes, partly as a result of the belief that it increases fertility, partly as a ceremonial ; but since many of the earths are rich in salts of iron, calcium, magnesium and sodium, there may be a physiological basis for earth-eating.

The author believes that there is some degree of toxaemia in hookworm disease, which, in a few cases, may be responsible for fever, eosinophilia and oedema, when these cannot otherwise be explained. *Charles Wilcocks.*

ROGERS, A. M. & DAMMIN, G. J. **Hookworm Infection in American Troops in Assam and Burma.** *Amer. J. Med. Sci.* 1946, May, v. 211, No. 5, 531–8.

Differing from the traditional picture of hookworm disease, the prominent features in 50 consecutive cases in combat troops in North Burma were gastro-intestinal symptoms, of abrupt onset, and lack of anaemia. There were nausea and vomiting with abdominal pain, usually epigastric, arising immediately after meals and not relieved by food. Diarrhoea was a prominent sign, but blood, pus and mucus were not found in the stools. By questioning, a history of ground itch was obtained from a quarter of the patients, and a history of respiratory symptoms from 70 per cent., but the value of these histories is doubtful. All the patients had lost some weight, ranging from 10 to 40 lb., but loss of weight was common among all combat troops in Burma. Some patients had a low-grade fever, and a few had attacks of urticaria. A striking feature of the infection was the degree of eosinophilia, the discovery of which first led in many instances to the examination of the stools. The maximum eosinophilia was 70 per cent., with a total leucocyte count of 41,000 per cmm., but the more usual finding was eosinophilia of 40 per cent. with a total count of about 15,000 leucocytes. The earliest time for appearance of eosinophilia after the suspected date of infection was 30 days, and the eosinophilia persisted to a diminished degree for weeks and months, despite frequent vermifuge treatment. Anaemia was neither marked nor constant.

Direct examination of the stool revealed initially only 20 per cent. of the infections, but by repeated direct examinations it was possible to establish the diagnosis in a little more than half the patients. The zinc sulphate flotation-centrifugation method increased the number of positive findings four-fold, and

proved a rapid and efficient means of finding eggs in the stool ; in all cases the diagnosis was confirmed by the finding of eggs by one or other of these methods.

The routine treatment consisted of 3 cc. of tetrachlorethylene, given in the morning, after a fat-free supper followed by a magnesium sulphate purge on the previous evening ; a second purge was given 2 hours after the vermifuge. If treatment failed, it was repeated after an interval of 3 weeks. Sometimes carbon tetrachloride or hexylresorcinol was used. One week or more after treatment the stools were re-examined ; 20 per cent. of the patients still showed eggs, although, on the average, they had been treated twice.

The anorexia, vomiting and diarrhoea were most readily relieved by treatment, while the cramping pain after meals was the slowest symptom to disappear, and the one which persisted in those who were unimproved.

It should be pointed out that not all the patients showed the acute syndrome described, and in fact many asymptomatic infections were discovered by the routine examination of the stools of patients admitted to hospital for some other condition. *F. Murgatroyd.*

STUBENBORD, W. & ALLEN, R. F. **Hookworm Disease in Infants. Report of Two Fatal Cases.** *U.S. Nav. Med. Bull.* 1946, June, v. 46, No. 6, 915–17.

Hookworm disease is rare in infants under one year of age, partly because they do not often come into contact with infected soil. The author records two cases from Guam, in which massive infection was present in such infants. In the first infant, moribund on arrival at hospital, 300–400 adult *Ancylostoma duodenale* were present in the intestine, the child was anaemic, and there was fluid in the pleural and abdominal cavities. In the second (dead on arrival at hospital) there were several hundreds of *A. duodenale*, many haemorrhagic areas in the mucosa of the small intestine, and extreme anaemia.

Charles Wilcocks.

SCOTT, J. A. **Simplified Quantitative Methods for Hookworm Control Programs.** *Amer. J. Trop. Med.* 1946, May, v. 26, No. 3, 331–7, 1 fig.

The final answer to the problem of the control of hookworm disease is improvement in environmental sanitation. In Georgia, sanitation programmes have not yet reached the families most affected, and are unlikely to do so for many years ; interim measures are therefore necessary.

The public health authorities have aimed at treating the most heavily infected members of the community, with the objects of obtaining the maximum reduction in the source of infection and of relieving the symptoms in those most affected.

" It is now generally agreed that the pathogenicity of hookworms is fundamentally based on their blood-letting activities, that anemia is the primary symptom, and that all other manifestations are secondary to it. The extent to which the severity of anemia is related to the intensity of hookworm infection is often obscured, however, by a nutritional factor. Apparently, most well nourished persons have enough immunity to prevent the establishment in the intestine of hookworms in numbers sufficient to cause appreciable anemia. In certain states of malnutrition this protective mechanism is weakened and large numbers of worms become established. Moreover, this nutritional imbalance may of itself cause anemia. Hookworm disease is, then, primarily the result of the additional drain which the worms place upon a hemopoietic system already nearing, if not past, its maximum limit of compensatory reaction. In evaluating the seriousness of hookworm disease, there are two factors to be considered. The first is a determination of the degree of anemia,

which can be accurately done by the use of a hemoglobinometer, or approximately estimated from the clinical signs. The second is a necessity for determining what portion of the anemic condition is due to the basic state of malnutrition and what portion to the superimposed hookworm infection. HILL and ANDREWS [this *Bulletin*, 1943, v. 40, 324] showed that in Georgia no measurable depression of the average hemoglobin reading was associated with hookworm egg counts of less than 2,500 per cc. [the figure, corrected for the consistency of the stools, was 5,000 per cc.]. Above this point, however, a progressive drop in the hemoglobin reading was correlated with the size of the egg count. From these data it was concluded that in Georgia all of the cases of hookworm disease would be found in the group whose counts were above 2,500 eggs per cc. In practice, the order of making these determinations is reversed."

In annual examinations of the schoolchildren, the clinically grossly anaemic are selected, the border-line cases are checked by haemoglobin examination, egg counts are made on all anaemic children, the families of children with more than 2,500 eggs per cc. of stool are visited, and those found infected are treated.

There are limitations to the accuracy of this method of selection, and further it involved the use of statistical methods which are not simple enough for general application in a health programme. In this paper a modification of this procedure is described.

" The data are based on the examination of specimens collected from rural, white families by a visiting nurse. These families were chosen at random from over the whole country, except for the fact that obviously well-to-do families were not included. Specimens were examined by a salt flotation method and the positives were re-examined by egg count, using the technique as modified by Stoll and Hausheer."

After some necessary adjustments have been made owing to the fact that it was not possible to do egg counts in every case in which the floatation method showed eggs, the data are arranged as in the example given below. [While the adjustments that were made would satisfy most statisticians, it seems that they could have been obviated by the collection of larger samples of stool in every case.]

Hookworm infection in Brantley County, Georgia, in 1942.

Age Group	No. of persons examined	Percent. infected with hookworm*	Percent. positive by egg count†	Percent. of suspected cases of hookworm disease ‡
0–4	160	49·4	45·6	23·4
5–19	514	67·7	63·8	32·6
20+	150	46·7	38·2	11·3

* Per cent. positive by flotation. † With 200 or more eggs per cc.
‡ With 2,500 or more eggs per cc.

This table gives all the important data for the practical use of the health officer, but for the use of the statistician, for comparison with data in which different levels of significance have been used, further calculations have to be made. The author shows how a normal curve based on the figures of the fourth and fifth columns of the table approximate very closely the normal curve based on the entire series of egg counts, and he therefore considers that these two figures will supply sufficient data for most statistical purposes.

L. E. Napier.

i. Rocha e Silva, M. & Graña, R. **Anaphylaxis-like Reactions produced by Ascaris Extracts. I. The Change in Histamine Content and the Coagulability of the Blood in Guinea Pigs and in Dogs.** *Arch. Surgery.* 1946, May, v. 52, No. 5, 523–37, 4 charts. [Refs. in footnotes.]

ii. —— & ——. **II. The Mechanism of the Shock induced in Dogs.** *Ibid.* 1946, June, v. 52, No. 6, 713–28, 6 charts. [Refs. in footnotes.]

iii. ——, Porto, A. & Andrade, Sylvia O. **III. The Role played by Leukocytes and Platelets in the Genesis of the Shock.** *Ibid.* Aug., v. 53, No. 2, 199–213, 3 figs. [20 refs.]

i. In an earlier paper (to be published) the authors studied the mechanism of shock produced by hydatid fluid injected into dogs, and concluded that the substance which caused the shock is not precipitated by 5 per cent. trichloracetic acid, does not dialyze through Cellophane paper, and resists boiling for "a long time". They obtained a fairly well-purified material which produces profound shock in dogs, the shock being indirect, because a second injection produces no appreciable effect (desensitization). In some instances they also found an evanescent incoagulability of the blood (complete incoagulability in some animals) which suggested the liberation of heparin from the tissues into the blood. They found that histamine in the circulating blood of a few animals was increased, but that in most of the animals the histamine in the blood was decreased, although Graña *et al.* found that histamine was increased in every dog into which hydatid fluid was injected. The authors decided to find out whether nematodes may contain substances which produce shock.

Leroy (*Arch. Internat. de Physiol.*, 1910, v. 9, 276) and Emery and Herrick (*Amer. J. Physiol.*, 1929, v. 91, 143) found that extracts of *Ascaris lumbricoides* produce hypotension in dogs. Shinamura and Fuji (*J. Coll. Agric.*, 1917, v. 4, 189), quoted by Essex, Markowitz and Mann (*Amer. J. Physiol.*, 1931, v. 98, 18) isolated an "albumose-peptone", which was very toxic to dogs and called this substance "askaron". Machebouef and Mandoul (*C. R. Soc. Biol.*, 1939, v. 130, 1032) produced in guineapigs, with extracts of *A. lumbricoides*, emphysema not distinguishable from that produced by anaphylactic shock. The material which did this was soluble in 4 per cent. trichloracetic acid and in 50 per cent. ethyl alcohol and it was not removed by dialysis. Bier (personal communication to the authors) showed in 1939 that a substance in *A. lumbricoides* produces shock resembling anaphylactic shock in guineapigs. The present authors observed that extracts of *A. lumbricoides* produce severe or fatal shock in dogs, which has features of anaphylactic shock, namely, liver congestion, incoagulability of the blood, desensitization after recovery, and the appearance of histamine in the blood. The shock is, however, very severe and nearly all the dogs react violently to a few cubic centimetres of the extract.

The material used for the experiments here described was obtained from *Ascaris lumbricoides* ground in a colloid mill, the pulp obtained being treated with an equal volume of 10 per cent. trichloracetic acid for 2 hours at room temperature and then left overnight in the refrigerator. The opalescent fluid thus obtained was dialysed through cellophane for at least 48 hours until it was freed from trichloracetic acid. The *p*H was then adjusted to neutrality with sodium carbonate, and the fluid was used. For details of the further purification of this material the paper itself must be consulted. The tests done suggested that the substance causing shock in dogs is not a protein, but a proteose of large molecular weight. A glycogen fraction was also prepared, which was apparently related to the polysaccharide prepared from *A. lumbricoides* by Campbell (*J. Infect. Dis.*, 1936, v. 59, 266). Antithrombin assays

of the blood of the dogs were done with a solution of human prothrombin prepared by the method of Quick (*Amer. J. Physiol.*, 1936, v. 116, 535).

For details of the experiments done and for the authors' comments upon them the paper itself must be consulted. The authors found that deproteinized and dialysed extracts of *A. lumbricoides* produce a severe form of shock in dogs, accompanied by enormous engorgement of the liver, drastic reduction of the liver histamine, increased histamine in the blood, the appearance of "an antithrombin (heparin) factor" in the circulating blood, and desensitization. The main increase of blood histamine occurred in the "portal vein", the histamine content of the blood in this vein being in many instances two to six times higher than that in the femoral vein. Crude extracts of *A. lumbricoides* produced massive emphysema in guineapigs and death in a few minutes. In a few guineapigs increase of the blood histamine was observed.

The authors discuss the allergic nature of this anaphylaxis-like reaction. Most of the dogs used had heavy infections with intestinal hookworms and injection of *Ascaris* extracts produced skin reactions, so that it is possible that most of the dogs in Brazil are sensitized by intestinal nematodes and that this sensitization is allergic rather than anaphylactic. The authors emphasize their view that a distinction cannot be drawn between allergy and experimental anaphylaxis.

ii. In their second paper the authors record experiments which follow up the work recorded in their first paper, which showed that injection of *Ascaris* extracts into the veins of normal dogs causes a discharge of histamine into the general blood circulation. Because there is considerable decrease of the total histamine which can be extracted from pieces of liver taken after the shock produced by the *Ascaris* extracts has occurred, the authors conclude that most of the histamine discharged into the blood during the shock comes from the liver. In this second paper experiments are, however, recorded which show that the *Ascaris* extracts cannot cause a discharge of histamine from the livers of dogs previously sensitized by two subcutaneous injections of the *Ascaris* material, when these livers were perfused with Tyrode solution or defibrinated blood. Two of the dogs used for these experiments had been previously sensitized to horse serum, but the perfusion of horse serum through their livers did not cause a discharge of histamine. The authors therefore concluded that direct contact of the antigen with the sensitized liver cells is not enough to cause discharge of histamine. "In identical circumstances" trypsin and mercury bichloride perfused through the livers regularly caused a discharge of "copious amounts" of histamine.

The authors also describe in this paper a "mechanical" type of shock observed in about 5 per cent. of the dogs into which *Ascaris* extracts were injected. This form of shock is characterized by a profound fall in the blood pressure in the carotid artery, but no increase of the blood histamine or heparin. Apparently it depends upon a mechanical obstruction of the hepatic blood vessels by clumped leucocytes and blood platelets, "without very much discharge of active substances."

Experiments are also described which indicate that the intravenous administration of liver glycogen partially or completely desensitizes the animal to the *Ascaris* extract, and that the discharge of histamine and heparin from the liver cells can be entirely prevented by the administration of glycogen. The authors adduce as the explanation of this inhibition the fact that liver glycogen almost entirely removes platelets from circulating blood, and causes severe leucopenia.

iii. The authors of this paper follow up the conclusion of Rocha e Silva and Graña (see ii above) that the contact of *Ascaris* antigen alone with

the cells of the liver of the dog is not enough to produce an appreciable discharge of histamine from the liver cells. They claim that they have shown that the blood contains all the constituents which are necessary to do this when *Ascaris* antigen is added to the system.

The preparation of the *Ascaris* extracts and the method of perfusing the liver were those which were described in the earlier papers, except that the blood (800 cc.) used for perfusion was collected over a 3·8 per cent. solution of sodium citrate (200 cc.) in a paraffined beaker. For the methods of estimating the velocity of the perfusion, the number of the blood platelets and the amounts of histamine, heparin and plasma trypsin the paper itself must be consulted.

The authors conclude from all their results that the shock produced by *Ascaris* extracts and anaphylactic shock " have the same mechanism ". When the isolated liver of the dog is perfused with citrated whole blood contained in paraffined receptacles a conspicuous decrease of the leucocytes and blood platelets follows the injection of *Ascaris* extracts into the cannula. Usually small amounts of histamine and of an anticoagulant (heparin) are released into the perfusing blood and in one instance considerable amounts of both were discharged from the perfused liver. " This definitely shows that intact blood contains the factors which are necessary to produce a release of histamine and heparin from liver cells when the [*Ascaris*] extract is added."

Microscopical examination of smears made from pieces of liver taken before and after the shock in the intact unanaesthetized dog showed that platelets formed enormous aggregates which disappeared or partially disintegrated during the later stages of the shock. Plasma trypsin, free and total, was estimated in the blood used for perfusion before and after injection of the *Ascaris* extracts. Similar estimations were made in the circulating blood of the intact dog which was given *Ascaris* extracts intravenously. Although, in a few instances, there was a clear indication of the activation of plasma trypsin, usually there occurred, especially at the height of the shock, a definite decrease of free trypsin. This decrease of free trypsin was attributed to the appearance of heparin in the circulating blood. The authors discuss the probable chain of reactions which leads to the discharge of histamine and heparin from the parenchyma of the liver of the dog during anaphylactic shock and give a diagram of these. They also discuss the correlation between these reactions and the clumping and disintegration of blood elements, especially the platelets, which occur in the liver capillaries. *G. Lapage.*

Clemo, G. R., Cocker, W. & Hornsby, S. **The Constitution of Santonin. Part IV.** *J. Chem. Soc.* 1946, July, 616–17.

Wharton, D. R. A. & Stelma, T. **Comparative Cutaneous Tests for Filariasis with Antigens of Different Dilutions.** *J. Infect. Dis.* 1946, Jan.–Feb., v. 78, No. 1, 49–59. [11 refs.]

It is not possible to summarize here the interesting details contained in this paper. The publication and discussion of them are valuable, because they illustrate important sources of error against which those who attempt cutaneous tests with filarial antigens have to guard. This abstract may advantageously be read together with that of Warren *et al.* printed below.

The authors of the present paper summarize some of the relevant literature and point out that the cutaneous test for filariasis has two weaknesses—it cannot differentiate between infections with the different species of filarioid nematodes parasitic in man, and some 10 per cent. of the tests done give false

positives (see, however, below). The antigen used was prepared from vacuum dried specimens of *Dirofilaria immitis* ground up with saline to make a dilution of 1 : 100. This dilution was then frozen and thawed alternately twice during one day, heated for four hours at 56°C. and centrifuged at 2,500 r.p.m. for 30 minutes. The supernatant extract was then fractionally sterilized at 56°C., tested for sterility, phenolized to 0·3 per cent. and diluted with physiological saline for use. The authors think that the general opinion is that the immediate reaction is the significant one and that the index of the strength of the reaction is, in the following order, erythema, weal, a weal with pseudopodia, singly or in combination ; but various authors have varying criteria of the strength of the positive reaction. The present authors made their injections on the flexor surface of the forearm at a distance of 10 cm. apart, but even when this was done, the swelling and erythema of delayed reactions sometimes became confluent with the areas into which weaker dilutions of antigen and the control fluid were injected. The control fluid was dog serum fractionally sterilized at a dilution of 1 : 100, preserved with 0·3 per cent. phenol and used at the same dilutions as those of the filarial antigen. Delayed reactions resulted when the stronger antigens were used. These could begin as early as one hour after the injection, but did not develop in one case until three days after it. In some cases the arm was incapacitated by the delayed reaction. The delayed reaction in filariasis usually develops rapidly and is a deep, extensive, swollen, erythematous, "rubbery" zone which itches and feels heavy. Fairley identifies it with Calabar swelling.

Four series of subjects were used, numbering 286 in all. Series 1 were 29 filarious seamen from the Dutch West Indies together with 4 other members of the same ship's crew from the same endemic area. These men were tested with antigen dilutions of 1 : 1,000 and 1 : 8,000. Series 2 acted as controls of series 1 and consisted of 54 non-filarious individuals from the Allergy Clinic of the New York Hospital, all of them being allergic to various substances. Series 3 was composed of 153 individuals, some of whom had a history of filariasis or had been exposed to infection in an endemic area, and most of whom were allergic to various substances. These were tested with high dilutions of 1 : 20,000 up to 1 : 800,000, a dose of 0·02 ml. of the antigen being given. The dog serum control fluid used to test this series was diluted to 1 : 100,000 and no phenol was used in any of the fluids injected. Series 4 consisted of 46 men under observation for filariasis or other infections acquired in the South Pacific. These were tested with dilutions of 1 : 1,000 to 1 : 100,000 of the antigen and 1 : 10,000 of the dog serum control fluid, the doses injected being 0·02 ml.

The authors claim that the results indicate that a dilution of 1 : 8,000 of the antigen used, given in a dose of 0·01 ml., is an effective antigen, but that it does not, as Bozicevich and Hutter [this *Bulletin*, 1944, v. 41, 1055] claimed, screen out false positives, because the present authors, in the tests of Series 2, obtained with this dilution 5·6 per cent. of false positives. When, however, the 1 : 100,000 dilution was tested on Series 3, only 2 per cent. of false positives were obtained. This dilution gave, on the other hand, positive tests with only 80 per cent. of infected persons, so that it may need to be supplemented with a dilution of 1 : 20,000. The higher dilution is less likely to produce the objectionable delayed reaction mentioned above. The results show that it is essential to use dog serum as a control. The authors found no evidence of a cross reaction in persons infected with other species of parasitic animals, which included malarial parasites, *Entamoeba histolytica*, hookworms, whipworms and *Giardia*. Unlike Bozicevich and Hutter, the authors could not find any evidence that the filarial substance used was toxic when large amounts (250 mgm. of the residue after centrifugation of the saline extracts of worm substance and the equivalent of 1·0 gramme of whole worm powder per animal) were injected into rabbits. Filarious cotton rats (*Sigmodon hispidus littoralis*), infected with the filarioid

species *Litomosoides carinii*, tolerated massive doses of *Dirofilaria immitis* material (up to 25 mgm. of powdered *Dirofilaria immitis* in physiological saline). When death of these rats was caused by higher doses it appeared to be due to anaphylactic shock. *G. Lapage.*

WARREN, Virginia G., WARREN, J. & HUNTER, G. W. **Studies on Filariasis. I. Serological Relationships between Antigenic Extracts of** *Wuchereria bancrofti* **and** *Dirofilaria immitis*. *Amer. J. Hyg.* 1946, Mar., v. 43, No. 2, 164–70, 1 fig. [12 refs.]

The authors set out to seek, for the diagnosis of filariasis, a better test than biopsy or the discovery of microfilariae in the blood. They summarize the contents of several papers, all of which have been abstracted in previous issues of this *Bulletin*, which record results obtained with antigens obtained from the filarioid species *Dirofilaria immitis*, *Litomosoides carinii* and *Contortospiculus rheae*. The authors say that it is generally agreed that extracts of these species will give cutaneous reactions in persons infected with *Wuchereria bancrofti* and that precipitin and complement-fixation tests done with them are also successful to a certain degree. Antigens have also been made from *Wuchereria bancrofti* [see ACTON and RAO, this *Bulletin*, 1933, v. 30, 699] and OLIVER-GONZÁLEZ and BERCOVITZ [this *Bulletin*, 1945, v. 42, 219], but these gave disappointing results.

The present authors made antigens from the microfilariae of *W. bancrofti* and also from adult *D. immitis*. They describe in detail the methods used for making them. Microfilariae of *W. bancrofti* were isolated from human blood by centrifugation, frozen, dried *in vacuo*, powdered, dried again over $CaCl_2$ and a 1 per cent. suspension was then made in physiological saline. This was refrigerated at 5°C. for 24 hours and then alternately frozen and thawed several times and put in a water bath at 56°C. for 4 hours and often shaken to decrease "any anticomplementary properties." It was then centrifuged at 500 r.p.m. for 10 minutes. The process was sterile throughout. The resulting supernatant fluid was used as the antigen, being preserved by the addition of 0·3 per cent. phenol. The sediment was used for the immunization of rabbits. The control fluid was a "leucocyte-stroma antigen" made in the same way from normal human blood known to be free from microfilarial larvae. The *Dirofilaria immitis* antigen was made from dried adult specimens obtained from the heart and lungs of dogs. With these antigens the authors did complement-fixation tests, intradermal tests and studies of cross antigenicity. For the details of the technique of these experiments the paper itself must be consulted.

Complement-fixation tests were done upon the sera of 12 subjects who had been clinically diagnosed as suffering from filariasis. Antigen dilutions of 1 : 100 and 1 : 800 were used with serum dilutions of 1 : 1 and 1 : 128. All the sera gave negative results with the *W. bancrofti* antigen, even though motile microfilarial larvae were present in two of these sera. All the sera, on the other hand, gave strongly positive fixation with the *D. immitis* antigen. The former antigen thus appears to be unsuitable for complement-fixation tests. The authors thought that the failure of the *W. bancrofti* antigen might have been due to the use of an antigen deficient in a water-soluble component lost in the washings of the citrated blood used, but all attempts to make an antigen containing this water-soluble component, or to make a polysaccharide antigen, failed to produce an antigen which would give positive results.

Intradermal tests were done on 32 soldiers who had recently returned from a hyperendemic area in the Southwest Pacific; they showed "good clinical evidence" that they were suffering from filariasis. The sera of 30 of these men gave positive fixation with *D. immitis* antigen, but microfilarial larvae

were not found in the blood. Each man was given an injection of 0·025 ml. of dilutions of 1 : 4,000, 1 : 8,000 and 1 : 12,000 of the *W. bancrofti* antigen, and dilutions of 1 : 8,000 of the *D. immitis* antigen. Control tests were done with 1 : 4,000 dilutions of the leucocytestroma antigen and with 1 : 8,000 dilutions of dog serum in physiological saline to which 0·3 per cent. phenol had been added. The criterion of a positive reaction was a weal which had at the end of 10 minutes a diameter at least 3 mm. greater than that of the control.

Of the 32 subjects, 22 gave positive reactions to the *W. bancrofti* antigen, 23 were positive to the *D. immitis* antigen, 17 were positive to both and 4 to neither. Two subjects, whose sera gave no complement fixation to *W. bancrofti* antigen and yet contained microfilarial larvae, gave positive intradermal reaction to *W. bancrofti* antigen and strongly positive ones to *D. immitis* antigen.

When 75 control subjects with a history of allergy were tested, none of whom had been in an endemic area, only four of them gave a "cutaneous response" to *W. bancrofti* antigen. When 21 others infected with "intestinal nematodes," the species of which are not given, were tested, none gave a positive intradermal reaction with *W. bancrofti* antigen.

In order to explain the discrepant results obtained with these two antigens the authors tried to prepare specific antisera. Four rabbits were immunized with 1 : 100 dilutions of both antigens and with sediments of worm material obtained from the centrifugation during the preparation of the antigens. Two rabbits were given the *W. bancrofti* sediment and two were given the *D. immitis* sediment, all having 10 injections intraperitoneally. The sera of these rabbits were then titrated against the antigens and against the human leucocyte-stroma antigen for complement fixation. With both antigens a high titre occurred, but the antisera also reacted to an equal degree with the leucocyte-stroma antigen. No fixation occurred, however, when normal rabbit sera were used.

To study cross-antigenicity one portion of a high-titre *W. bancrofti* serum was absorbed for 18 hours at 5°C. with an excess of *W. bancrofti* antigen, a second portion with an excess of *D. immitis* antigen and a third with the leucocyte-stroma antigen. Similar absorptions of a high-titre *D. immitis* antigen were done, but none were done with the leucocyte-stroma antigen. It was found that absorption of antisera with the homologous antigen removes all activity from the immune sera, but that absorption with the heterologous antigen removes only the heterologous antibody. The authors concluded that both the filarial species used contain a species-specific and also a group-specific antigen. *G. Lapage.*

Sutliff, W. D. & Antonio Echandi G., R. **Pinworm (*E. vermicularis*) and other Intestinal Parasites in Costa Rican Children.** *J. Parasitology.* 1946, June, v. 32, No. 3, 233–6. [11 refs.]

Dorin, R. P. **The Preparation and Demonstration of an Antiserum for *Trichinella spiralis*.** *J. Parasitology.* 1946, Feb., v. 32, No. 1, 83–6.

The author describes the fixation of *Trichinella spiralis* antigen on to aluminium cream preparations by the method originally described by Hektoen and Welker (*J. Infect. Dis.*, 1933, v. 53, 309) and used successfully "in the field of organ-sera" by Spinka and Weichselbaum (*Proc. Soc. Exper. Biol. & Med.*, 1938, v. 38, 447), Mann and Welker (*Amer. J. Cancer*, 1940, v. 39, 360) and Cohen and Freda (*Proc. Soc. Exper. Biol. & Med.*, 1940, v. 43, 22). The author claims that the method makes possible a single injection of

the antigen and the use of material which need not be sterile, and that the rabbit into which it is injected produces antibodies for a long while.

The author used larvae of *Trichinella spiralis* isolated from rat muscle by digestion, and washed in physiological saline until the Biuret test was negative. If, he says, this washing is not done, the experimental animal dies, possibly from peptone shock. The larval material was then absorbed on to aluminium cream by the method of WELKER and TRACY (*J. Biol. Chem.*, 1915, v. 22, 55). The material thus obtained was then injected into rabbits by the method of Hektoen and Welker. Variations in the method of making the antigen resulted in the production of different titres in the antisera obtained, and these are discussed by the author. The antigen used to find the titre of the antisera was a commercial preparation made by the Eli Lilly Co. and used for intradermal tests in the diagnosis of trichiniasis. This antigen was adjusted to neutrality with acetic acid and its nitrogen content was determined by the Koch-McMeekin micro-Kjeldahl method. The author found that this antigen did not give a positive reaction with an antiserum made from rat tissue by the method of Spinka and Weichselbaum. None of the rat tissue antisera reacted positively with rat tissue autolysates made by the method of Mann and Welker. The antisera were usually made by the method of Spinka and Weichselbaum. It was found that the injection of a suspension of 400,000 *Trichinella* larvae in 80 cc. of saline with the addition of 120 cc. of aluminium cream gave, after centrifugation, the desired amount of material for injection into each rabbit. Each rabbit thus received 400,000 *Trichinella* larvae.

Injection of these antigens gave antisera with titres of : 1 : 4,000, 1 : 5,000, 1 : 6,000 and 1 : 11,000. When rabbits were given by the mouth doses of larvae near the lethal dose, antisera were obtained with titres ranging up to 1 : 8,000, according to the length of time since the injection.

The effect of the injection of these antigens upon the resistance of rabbits to infection with *Trichinella spiralis* was striking. Three rabbits were injected with antigen fixed on aluminium cream, and these were used as actively-immunized animals. These and also five normal rabbits as controls were each given by the mouth 20,000 *Trichinella* larvae in 10 cc. of saline. Two of the controls died and one of the immunized rabbits died on the 32nd day from the effects of a bite by one of its mates. The others were killed on the 43rd day after the doses of larvae and equal weights of their muscles (tongue, masseters, diaphragms and muscles of the two forelegs) were digested. In one immunized rabbit the only larvae found were the ten in the muscles of one of the forelegs ; the titre of the antiserum of this rabbit was 1 : 6,000. In the other immunized rabbit 90 larvae were found in the tongue, 120 in the masseters, 150 in the diaphragm, 200 in the muscles of one foreleg and 800 in those of the other ; the titre of the antiserum of this rabbit was 1 : 5,000. In the controls from 7,800 to 12,000 larvae were found in the tongue, from 16,900 to 23,700 in the masseters, from 16,400 to 32,700 in the diaphragms, from 30,500 to 45,000 in the muscles of one of the forelegs and from 30,700 to 47,500 in those of the other. The conclusion was drawn that the actively immunized rabbits had resisted the infection.

It was found that injection of the immune sera also protected the rabbits. Six rabbits were given a sublethal dose of 4,500 *Trichinella* larvae. Three of them were then given 9 cc. of immune serum intraperitoneally in doses of 3 cc. each, one on the day before the larvae were given, one on the day on which they were given and one on the day after they were given. The three other rabbits were given normal rabbit serum in the same way. Two uninfected rabbits were given the same amount of normal serum as an additional control. Eleven days later it was found that (*a*) the rabbits given larvae and immune serum were sleek, active, responsive and clean-looking, and apparently normal ;

(*b*) the rabbits given larvae and normal serum had " bloody-red noses " and ruffled fur, and were unresponsive and apparently moribund ; (*c*) the controls given normal serum only were normal. The conclusion was drawn that the immune serum had protected the rabbits. The author claims that the antisera are specific to larvae of *Trichinella spiralis*, but not for any of the host proteins. *G. Lapage.*

Leon, L. A. Cuarto caso de infección humana por Agamomermis. [**Fourth Case of Human infection with** *Agamomermis.*] *Rev. Med. Trop. y Parasit.* Habana. 1946, Jan.–Mar., v. 12, No. 1, 25–6, 3 figs.

This paper describes a nematode found in the excreta of a mestizo child aged five, who came for treatment for infection with *Ascaris lumbricoides*. The nematode is briefly described and the author regards it as a species of " *Agamomermis* ", a name given to immature forms of species belonging to the nematode family Mermithidae, which have been found in the past three times in human beings and are noted in text-books of parasitology. All are regarded as accidental parasites, and the specimen here described is regarded by the author as an accidental parasite ingested with the food, possibly with raw fruit. [The Mermithidae are nematodes whose larval phases are parasitic in earwigs, grasshoppers and some other insects, the adult phases being non-parasitic and living in the soil. " *Agamomermis* " should not be confused with *Agamermis*, which is the name of a true genus of the family Mermithidae.] *G. Lapage.*

DEFICIENCY DISEASES.

Clarke, C. A. & Sneddon, I. B. **Nutritional Neuropathy in Prisoners-of-War and Internees from Hong-Kong.** *Lancet.* 1946, May 18, 734–7. [Summary appears also in *Bulletin of Hygiene.*]

This report deals with the condition, after their arrival in Australia, of 200 patients who had been prisoners in Hong Kong from late 1941 until September 1945. On admission to hospital none of the patients showed any of the classical signs of vitamin deficiency, but 74 of them showed grossly abnormal neurological signs, which were classified as optic atrophy and ataxic paraplegia in 31 patients, ataxic paraplegia alone in 21, optic atrophy alone in 13, optic atrophy, nerve deafness and ataxic paraplegia in 6, and optic atrophy and nerve deafness in 3.

The commonest neurological abnormality was impairment of visual acuity (53 cases) due to central and paracentral scotomata : the ocular fundi showed partial optic atrophy, and in many cases macular degeneration was present. The paraesthesiae, sensory loss of stocking distribution, ataxia, foot-drop, and loss of deep reflexes were like those of polyneuritis, but tenderness of the calves was not found. Some cases showed increased deep reflexes, spasticity, and ataxia out of proportion to the degree of anaesthesia, and the condition of some suggested amyotrophic lateral sclerosis. No significant changes were found in the blood, nor was there any evident relationship between neurological disturbance and achlorhydria. No general lowering of the level of the plasma proteins was found, and oedema was never a prominent feature.

Treatment for two months with a high-calorie diet and massive doses of vitamins led to subjective improvements in many cases, but the neurological signs remained unchanged.

The authors believe that the neuropathy they describe results from a toxic or antivitamin principle in the diet rather than from a plain dietary deficiency. *H. E. Harding.*

PAGE, J. A. **Painful-Feet Syndrome among Prisoners of War in the Far East.** *Brit. Med. J.* 1946, Aug. 24, 260–62.

"The widespread occurrence of a distressing and serious syndrome among prisoners of war in the Far East, affecting the feet, with accompanying constitutional signs and known as the 'painful-feet' syndrome, is described. Owing to the lack of laboratory facilities, diagnostic aids, and controlled investigation, no satisfactory conclusions were reached as to the exact aetiology, but, from the study of a very large number of cases from the onset, the syndrome would appear to be the result of a deficiency of a factor or factors in the vitamin B complex closely allied to the P.P. factor, but primarily affecting the peripheral arteries of the lower extremities, or possibly be due to a toxic factor in old musty polished rice, associated with a low protein intake and reduced vitality.

"The appearances in the early stages, when redness and swelling of the feet were the predominant signs, are similar to those of erythromelalgia as first described by Weir Mitchell. It clearly is not an angioneurosis and is not associated with a neuropathic diathesis.

"The disease is amenable to treatment by replacement of the deficient elements in the diet, but otherwise is rapidly progressive, ending in death or serious crippling deformities."

MCDANIEL, F. L., WHITE, B. V., Jr. & THOMPSON, C. M. **Malnutrition in Repatriated Prisoners of War.** *U.S. Nav. Med. Bull.* 1946, June, v. 46, No. 6, 793–810, 3 figs. [17 refs.]

Three hundred and twenty men of the 1,520 released prisoners examined in Tokyo bay had sufficient physical disability to be placed on the sick list, and 53 of these were studied as the basis of this report. All had received a deficient diet, but the degree and the duration of deficiency varied considerably. Loss of weight varied from 30 to 70 pounds (13·5 to 32 kgm.), and weakness was the commonest complaint. Oedema was present in many of the men, but the total plasma proteins were normal in all but three. In a few of the patients oedema appeared after a full diet had been restored. In general, the oedema disappeared within a few days.

No signs were found indicating deficiency of vitamins A, C, or D; cardiac beriberi was shown by only one patient, and there was no definite pellagra. Numbness, tingling and pain were the commonest symptoms after weakness, and probably resulted from thiamin deficiency. Most of the patients showed a mild normochromic anaemia, claimed by the authors as due to sprue.

H. E. Harding.

MONTENY, V. A. R. Beriberi-Gevallen tijdens den veldtocht in Abyssinie. [**An Outbreak of Beriberi during the Campaign in Abyssinia.**] *Ann. Soc. Belge de Méd. Trop.* 1945, Dec. 31, v. 25, Nos. 3/4, 231–5.

The following is a translation of the author's summary :—

"A brief account of the symptomatology of a series of cases of beriberi among Congo troops camped at Gambeila, and belonging to the Belgian brigade which had operated in Abyssinia.

"Beriberi broke out as the wet form, and as an epidemic; it was the result of defective diet and of high atmospheric temperature to a mean of 50°C. (the dry season).

"The introduction of fresh fish, marmite, and sweetened milk into the diet, and the substitution of biscuits and bran for rice, put an end to the epidemic."

Charles Wilcocks.

ALLIBONE, E. C. & BAAR, H. S. **A Fatal Case of Beriberi in a Child in England.** *Arch. Dis. in Childhood.* 1946, June, v. 21, No. 106, 76–87, 18 figs. [31 refs.]

This is an interesting case of a boy who was first seen when three years old, and who died with anasarca and myocardial degeneration 5½ months later. The diagnosis of beriberi is based on the severe cardiac disease without valvular damage, and degenerative changes in the nervous system. There was also a raised level of pyruvic acid in the blood (1·8 mgm. per 100 ml. when first admitted, and 1·97 mgm. just over 5 months later).

If this diagnosis be accepted, however, the deficiency must have been a conditioned one, since his diet contained at least 0·75 mgm. thiamin a day when he was first seen, and this was increased to 0·9 mgm. a day plus some intermittent medication.

The first sign of illness before each of his two admissions to hospital was oedema of the legs, and on each occasion he was found to have very low figures for plasma albumin and globulin. The liver showed a rather peculiar cirrhosis, whose aetiology is not explained. [The condition of the liver may have been responsible for the metabolic disturbances. Certainly this is not a clear-cut case of beriberi.] *H. E. Harding.*

MICKELSEN, O., CASTER, W. O. & KEYS, A. **Urinary Excretion of Thiamine as a Characteristic of the Individual.** *Proc. Soc. Exper. Biol. & Med.* 1946, June, v. 62, No. 2, 254–8. [10 refs.]

Two groups, each of six normal young men, were maintained on diets containing respectively 1 and 2 mgm. thiamin a day. After a stabilizing period of a month, the excretion of thiamin and of pyramin was determined during two periods, each of 3 days.

Urinary excretion of thiamin on the constant diet given showed a 2- to 3-fold variation for the men in each group, and there was overlapping of the figures in the two groups. The excretion of pyramin was much more constant.

No correlation was found between the content of thiamin in the urine and in the faeces, nor with any of the physical characteristics of the individuals. The excretion of thiamin, however, was found to be a characteristic of the individual, as shown by the individual excretions remaining in the same rank throughout the 8 months of the full experiment, and at different levels of intake.

H. E. Harding.

HUNDLEY, J. M. & SEBRELL, W. H. **Electrocardiographic Alterations in Adult Rats as a Result of Acute Thiamine Deficiency.** *Pub. Health Rep.* Wash. 1946, June 14, v. 61, No. 24, 847–56, 15 figs. on 5 pls. [11 refs.]

"Nine-month-old rats developed a variety of electrocardiographic defects when they became acutely deficient in thiamine.

"The changes included bradycardia, sinus arrhythmia, sinus arrest, ectopic beats, delayed auriculoventricular conduction (PR), widened QRS complexes, bundle branch block, auricular fibrillation, idioventricular rhythm, notched, inverted, or otherwise variable P waves, inverted or diphasic T waves, and depression or elevation of the T-wave take-off.

"The response of these changes to thiamine therapy was variable. Some revert promptly and completely, others slowly or not at all."

TROWELL, H. C. **Malnutrition in Africans as an Indication of their Dietary Requirements.** *East African Med. J.* 1946, Feb., v. 23, No. 2, 34–43.

This paper is a general review of nutritional problems in East Africa, as seen through the eyes of a clinician. The author points out that classical deficiency diseases—scurvy, rickets, beriberi, and pellagra—are uncommon in East Africa. Clinicians, deceived by this, failed at first to recognize the widespread incidence of malnutrition. In recent years, facts have emerged to correct this error. In the first place, dietary studies show that the African's intake is inadequate by all recognized standards, and there is no reason to believe that his requirements are less than those of the European. Secondly, largely as a result of the author's own labours, a pattern of malnutrition different from the textbook syndromes, is gradually achieving recognition.

This pattern is most strikingly seen in children, under the name of kwashiorkor, but is also found in adults. The main features are loss of weight and failure of growth, depigmentation of skin and hair, dermatosis, oedema, anaemia, and diarrhoea, associated with radiological changes in the small intestine—"deficiency bowel pattern."

In discussing the practical conclusions that follow, the author points out that "all over Africa many children and adults attempt to satisfy their hunger only once or twice a day, and it is physically impossible to satisfy calorie requirements in this way." Diets should be planned to satisfy hunger three or four times a day, and should include a wide variety of foods. *J. Waterlow.*

HUGHES, W. **Achromotrichia in Tropical Malnutrition.** *Brit. Med. J.* 1946, July 20, 85–7. [13 refs.]

Two types of achromotrichia are described in Africans. One was associated with alopecia, and was seen in cases of kwashiorkor. The hair was thin and pale, and could be pulled out painlessly. Histological sections of the skin showed parakeratosis; it is suggested that continual loss of cells and pigment, as a result of hyperkeratosis, creates demands which the epidermis cannot meet. The recognized lesions of ariboflavinosis figure very largely in the kwashiorkor syndrome [HUGHES, this *Bulletin*, 1946, v. 43, 766; see also *ibid.*, 1946, v. 43, 581]. This suggests that the changes in skin and hair may also be caused by riboflavin deficiency.

In the second type of achromotrichia there was no alopecia, and the signs of ariboflavinosis were minimal. Eleven cases are described, in children aged 4–10 years. All were apathetic, anaemic, and showed some degree of oedema. The hair was white or grey, of finer texture than normal, and straight or wavy, instead of tightly curled. The hairs were brittle, but could not be pulled out painlessly at the roots.

On a diet containing liver, milk, and yeast, the general condition improved, and the growing hair came up strong, black and curly. This type of depigmentation is attributed tentatively to deficiency of pantothenic acid. One case showed no improvement on the ordinary hospital diet; in two cases in which this diet was supplemented with injections of calcium pantothenate, 25 mgm. daily, the hair began to come up black after three weeks. A fourth patient was given 300 mgm. of para-aminobenzoic acid daily, without effect. *J. Waterlow.*

NICHOLLS, L. **Grey Hair in Ill-Nourished Children.** *Lancet.* 1946, Aug. 10, 201, 2 figs.

The author has seen several cases in which greying of the hair of children aged 5–12 was associated with signs of multiple vitamin deficiency. The children were seen in Malaya, and most of them were Tamils; the hair of these people

is normally black. "Usually, only part of the hair is rusty, depending on whether malnutrition is of the present or was of the past." The hair was not finer or wavier than normal. Greying of the hair has been produced in animals, by giving them a diet deficient in pantothenic acid; autopsy in these animals shows necrosis of the suprarenal glands. Some degree of greying may arise from a deficiency of copper in the diet.

"Most of these children had been living largely on manioc root, and the vitamin deficiencies were multiple." On a good diet improvement was fairly rapid. *Charles Wilcocks.*

SPRUE.

KEELE, K. D. **A Study of the Onset and Cyclic Development of the Sprue Syndrome.** *Brit. Med. J.* 1946, July 27, 111–14, 5 figs.

The importance of sprue in India during 1943–5 is reflected by the fact that of 8,846 medical cases evacuated during that period, 1,073 were sufferers from sprue. The first 600 were studied under unfavourable conditions [see KEELE and BOUND, this *Bulletin*, 1946, v. 43, 368]. Though the symptoms of sprue are legion, they may be divided into two groups:—those at the onset consist of anorexia, diarrhoea, vomiting, weakness and loss of weight; diarrhoea is usually, but not invariably, first; then other symptoms follow during remissions of the symptoms of onset, these are glossitis, cheilosis, meteorism and scaling of the skin.

In untreated cases remissions of diarrhoea usually occur after a few weeks, with return of appetite which results in overeating, and relapse. It is claimed that during relapse glossitis and distension decrease in severity, but emaciation remains progressive. The symptoms of onset and relapse are similar; the symptoms of remission are different.

Anorexia consequent upon diarrhoea may be so pronounced as to be mistaken for anorexia nervosa. Vomiting is common. The stools are of normal colour at the onset, but become pale after a variable interval. They may be frequent, 15 to 20 a day. Their number, and response to sulphaguanidine therapy, have often led to the tentative diagnosis of bacillary dysentery. Asthenia occurs early, but is not accompanied by symptoms of effort syndrome. As compared with the normal weight-loss of service men in India (about 10 per cent.), that of sprue cases was up to 25 per cent. In the majority, dietetic therapy produces a change from relapse to remission (63 per cent. were treated dietetically).

In some of these, relapse symptoms persist—diarrhoea alternating with constipation and recurrent glossitis. Such static cases are turned into full remission by parenteral liver therapy, but it is remarked that in this event glossitis is always slight. The average duration of diarrhoea before the advent of glossitis is three months, and the latter appears at a period when relapse signs are decreasing and persists about two weeks in cases treated by dieting.

Emphasis is laid upon the transient nature of the tongue changes in early sprue; true depapillation is not present in early cases. Angular stomatitis and cheilosis are less common than tongue changes.

At onset and during relapse, abdominal distension is usually absent, especially in severe cases, but there is a remarkable increase of distension with response to treatment, and this coincides with cessation of diarrhoea and vomiting.

Scaling of the skin with loss of hair increases during remission. The scaling is general and the size of individual scales varies from fine branny desquamation to coarse plaques.

Signs of vitamin deficiency were observed, but in 20 cases with desquamation, 19 showed no evidence of deficiency of dark adaptation. It was noted that glossitis, angular stomatitis and scaling of the skin usually became accentuated even on a diet adequate in nicotinic acid and riboflavin. These and other observations do not lend support to the view that glossitis is related to nicotinic acid or riboflavin deficiency. Larval sprue (glossitis without steatorrhoea) was observed in 7·5 per cent.

Barium meal skiagrams showed that the emptying time of the stomach varied. In one severe relapse the barium clumped into large masses in the jejunum, but a month later, during remission, the mucosal pattern became normal.

Observations on the blood were made on venous blood drawn without stasis, using Wintrobe's mixture as anticoagulant. The degree of anaemia is not usually severe in early cases. Only some 24 per cent, had haemoglobin levels below 12 gm. per cent.; 26 per cent. showed macrocytic anaemia; 30 per cent. macrocytosis, but with normal haemoglobin and red cell count. Hypochromic anaemia was present in 9 per cent. Dehydration at onset and during relapse may mask the presence of anaemia by producing haemoconcentration. Conversely, in response to therapy, haemodilution may reveal an abnormal blood count. This is confirmed by plasma protein estimation. The degree of anaemia is not correlated with the degree of glossitis or achlorhydria. Liver therapy has less effect on the anaemia than on other symptoms of sprue. Reticulocytosis is poor and delayed, and is comparable with that found in tropical megalocytic anaemia.

Relapse with diarrhoea is accompanied by failure of absorption. In all cases fat absorption is grossly diminished, as judged by fat balances; sugar absorption is also diminished, as shown by flat blood-sugar curves; and electrolytes are deficiently absorbed, as judged by excess of faecal sodium with low blood levels.

In the remission phase chylomicron* counts become normal long before steatorrhoea disappears, whilst fat absorption does not improve in proportion to the clinical condition.

Rapid improvement of the stools occurs with liver therapy, which suggests marked increase of water absorption.

* Dorland's *Medical Dictionary* defines a chylomicron as "a particle of emulsified fat, about 1μ in diameter, found in the blood during the digestion of fat."

P. Manson-Bahr.

FOWWEATHER, F. S. & ANDERSON, W. N. **A Method for the Determination of Fat in Faeces.** *Biochem. J.* 1946, v. 40, No. 3, 350–51.

"1. A method for the determination of split and unsplit fat in faeces, by drying the specimen with plaster of Paris, extraction with light petroleum in a Soxhlet apparatus and subsequent titration of the extracted fat has been described. Probable sources of error have been dealt with.

"2. Comparison of the results by this method with those of a wet extraction method previously in use shows that the plaster of Paris method is efficient and satisfactory. Owing to the saving of labour involved, the plaster method is to be preferred to the wet extraction method."

HAEMATOLOGY.

HORECKER, B. L. **A Primary Standard for the Colorimetric Determination of Hemoglobin.** *J. Lab. & Clin. Med.* 1946, May, v. 31, No. 5, 589–94, 1 fig.

Determinations of haemoglobin suffer from inaccuracies or fading of the colour standards in the direct methods, and from changes in the calibration of the instruments in the photoelectric methods, while estimations depending upon chemical determinations are too cumbersome for the average clinical laboratory. Consequently, several methods based on the use of crystalline haemin as the primary standard have been suggested. The one here described, with a standard prepared by solution of crystalline haemin in N/10 borate buffer at *p*H 9·4, is superior to many in that the standard solutions are stable, have absorption spectra closely resembling that of alkaline haematin prepared from whole blood, and, as they do not react appreciably with glass, they can be kept in sealed tubes ready for use directly in the colorimeter for checking the calibration values.

Stock solutions of crystalline haemin, prepared from sheep's blood or obtained commercially, containing about 1 mgm. per cc., were made in N/10 buffer borate at *p*H 9·4, and, after ageing overnight, were diluted with borate buffer to give solutions of final concentrations ranging from 10 to 50 mgm. per litre. The stock solution should be discarded when a month old, and the dilute standards should be freshly prepared each day.

In the actual estimation, oxalated blood was converted into alkaline haematin by diluting the blood sample 1 : 251 in N/10 NaOH, heating for 5 minutes in a boiling water bath, and then immediately cooling ; under these conditions conversion of haemoglobin to alkaline haematin is complete and reproducible. The absorption spectra of the samples and standards were compared in a Beckman spectrophotometer using 10 mm. Corex cells and an effective slit width of 40 Å. Presumably because of the calcium oxalate formed, oxalated samples give a somewhat lower transmission than do non-oxalated samples. With blood diluted directly from finger puncture, the absorption values, and therefore the colour ratio, are about 3 per cent. lower. Comparisons were also made with portable photoelectric colorimeters and with an Evelyn colorimeter, using filters giving maximum transmission at 5,700 Å. The colorimetric calibrations were separated by a month, during which changes were made in an amplifier circuit, resulting in a higher sensitivity and a lower lamp temperature ; the transmission values were considerably different, yet there was no change in the value of the haemoglobin equivalent of the haemin standards.

The absorption of a solution containing 29·6 gm. crystalline haemin per litre of N/10 borate buffer at *p*H 9·4 is equal to that of a blood sample containing 16·7 gm. haemoglobin per 100 cc. blood diluted 1 : 251 in N/10 sodium hydroxide, with an accuracy within 0·2 gm. haemoglobin per 100 cc. *F. Murgatroyd.*

WILKINSON, J. F., ISRAELS, M. C. G. & FLETCHER, F. **Folic Acid in the Treatment of Pernicious Anaemia. Report of Five Cases.** *Lancet.* 1946, Aug. 3, 156–8, 2 figs.

Synthetic folic acid, a compound of 2-amino-4-hydroxy-6-methyl pteridine and *p*-aminobenzoylglutamic acid, was given to 5 patients with true pernicious anaemia in relapse. The drug was given orally in daily doses of 20 mgm., reduced after about the fourteenth day of treatment to 10 mgm. In one severe case 75 mgm. were also given, daily for two days, by intravenous drip, the drug being dissolved in water with the aid of disodium phosphate.

The responses seemed in every way comparable with those which might have been obtained with the best pre-war liver extracts. Reticulocytosis, return of the blood count towards normal level, restoration of the bone marrow from a megaloblastic to a normoblastic state, and clinical improvement occurred in each case. The achlorhydria persisted.

Folic acid is not the liver principle obtained in a very concentrated form by other means, because folic acid has an intense orange-yellow colour, whereas the purest liver principle preparations are colourless. *F. Murgatroyd.*

Robertson, E. I., Daniel, Louise J., Farmer, Florence A., Norris, L. C. & Heuser, G. F. **The Folic Acid Requirement of Chicks for Growth, Feathering and Hemoglobin Formation.** *Proc. Soc. Exper. Biol. & Med.* 1946, June, v. 62, No. 2, 97–101, 2 figs. [12 refs.]

Das Gupta, C. R., Ganguli, S. & Chatterjea, J. B. **Proteolysed Liver Extract in the Treatment of Tropical Macrocytic Anaemia.** *Indian Med. Gaz.* 1946, Mar., v. 81, No. 3, 122–6, 4 graphs. [15 refs.]

As an adequate protein intake appears greatly to help the recovery of patients suffering from tropical macrocytic anaemia, it was suggested that proteolysed liver extract, containing a considerable amount of protein in easily assimilable form, vitamins and the full amount of haematinic principle, would be an ideal preparation for the treatment of the disease.

The proteolysed extracts were prepared in the following way. Minced liver from freshly-killed healthy sheep or cows was mixed with half its volume of freshly-distilled water, and kept in a cold chamber overnight after adding 0·5 per cent. chloroform as a preservative. The following morning powdered papain, 2 gm. to the lb. of liver, and another half volume of distilled water were added, and the mixture was allowed to digest at 60°C. for 3 hours, at the end of which time it was boiled vigorously for 5 to 10 minutes. The hot mixture was then filtered through gauze, and the filtrate was cooled and concentrated, under reduced pressure, to one-third of its volume, alcohol 10 per cent. and glycerin 20 per cent. being added. Each fluid ounce of this extract represents approximately 50 gm. of raw liver. After being kept in a cold chamber for 2 to 3 weeks to precipitate unstable metaproteins, the mixture was filtered through Seitz pads, and the filtrate was sealed in sterile ampoules. The extract thus prepared keeps well in the cold chamber.

Fifteen cases of macrocytic anaemia were treated with the extract in oral doses varying from 30 to 90 cc. daily, for 10–44 days. It was well tolerated, even in the larger doses and even in the presence of diarrhoea.

All patients, except one who left hospital against advice, were considerably improved, and there was reason to believe that any effect from the normal hospital diet was only secondary. Sternal puncture, performed on 11 of the patients, showed that 9 originally had megaloblastic marrow, and 2 " dimorphic " erythropoiesis. The patients with the megaloblastic reaction in the marrow responded very well to the proteolysed liver extract ; the other two patients not so well. The anaemia showed improvement in the form of reticulocytosis, increase in the red cell counts and haemoglobin levels, and diminution in the mean corpuscular volumes, while high serum bilirubin values returned to normal. The gastric acidity did not appear to have any correlation with response to treatment, and the presence of intestinal helminthic or protozoal parasites did not seem to interfere with the response.

The results indicate that the missing haematopoietic factor associated with tropical macrocytic anaemia is present in appreciable amounts in proteolysed liver extract. *F. Murgatroyd.*

WATSON, Janet & CASTLE, W. B. **Nutritional Macrocytic Anemia, especially in Pregnancy. Response to a Substance in Liver other than that Effective in Pernicious Anemia.** *Amer. J. Med. Sci.* 1946, May, v. 211, No. 5, 513–30, 5 figs. [62 refs.]

Of 4 patients with nutritional macrocytic anaemia not responding to parenteral doses of liver extract adequate for the treatment of Addisonian pernicious anaemia, three showed a response to liver extracts given orally, and the fourth a response to liver extract parenterally when the dose was increased tenfold. This seemed to indicate response to a substance other than the haematopoietic factor presumably common to all liver extracts effective in Addisonian pernicious anaemia, as has been suggested frequently in the literature recording different responses, in nutritional macrocytic anaemia and Addisonian pernicious anaemia, to purified and crude liver extracts.

The four cases studied differed from Addisonian pernicious anaemia in that they had a marked history of dietary deficiency, and showed free hydrochloric acid in the gastric contents ; no neural manifestations or atrophy of the lingual papillae ; less macrocytosis, anisocytosis and poikilocytosis of the red blood cells than is usual in pernicious anaemia ; an unusually low percentage of reticulocytes ; and a normal icterus index. Furthermore, three of the patients who after treatment took no liver extract for over a year suffered no relapses.

From the differences in response it appears that at least two, and possibly three, types of nutritional deficiency are involved in nutritional macrocytic anaemias. There is a large group, including Addisonian pernicious anaemia and many cases of sprue and macrocytic anaemia of pregnancy, which respond to usual amounts of the most refined liver extracts administered parenterally. Then there are those cases which respond only to orally administered crude liver extracts or to large amounts of certain relatively crude liver extracts given parenterally. These anaemias include certain instances of tropical macrocytic anaemia, of anaemia of pregnancy, and of " refractory " anaemias with megaloblastic bone marrow. It is also possible that there was a difference between the deficiency responsible for the anaemia in two patients who responded to orally administered crude liver extract, and that responsible for the anaemia of two patients who responded to the large amounts of more refined liver extract. Wills first demonstrated a difference in the effects of refined and crude liver extracts in anaemic monkeys and later in patients. The " Wills' factor ", present in crude liver extracts and in autolysed yeast, differs from the liver principle which is effective in Addisonian pernicious anaemia, from the so-called extrinsic factor, and, according to observations by the present authors, from the various pure components of the vitamin B complex and accessory nutritional substances, including biotin, *L. casei* factor and pyridoxal.

In cases of macrocytic anaemia failing to respond to parenterally administered liver extract, especially those associated with pregnancy, a trial should be made of the efficacy of relatively crude liver extracts administered orally, or, when suitably prepared, administered intravenously in large amounts. It is possible that oral preparations may be of value in occasional patients classified as having " achrestic " or other refractory anaemias. *F. Murgatroyd.*

COOPERMAN, J. M., RUEGAMER, W. R. & ELVEHJEM, C. A. **Milk as a Source of the Monkey Anti-Anemia Factor.** *Proc. Soc. Exper. Biol. & Med.* 1946, June, v. 62, No. 2, 101–3.

FARBER, B. **Attack of Acute Hemolytic Anemia due to Favismo in a Young Child.** *Harefuah.* Jerusalem. 1946, July 1, v. 31, No. 1, 11. [In Hebrew.]

VENOMS AND ANTIVENENES.

GRASSET, E. La vipère du Gabon. Envenimation par *Bitis gabonica*. Son venin et sérothérapie antiveneuse spécifique. [**The Gaboon Viper,** *Bitis gabonica*. **Its Venom and Antivenene.**] *Acta Tropica*. Basle. 1946, v. 3, No. 2, 97–115, 8 figs. [15 refs.]

Bitis gabonica, known locally as *boma* or *teeya*, is one of the commonest African snakes and is met with in West, Central, and East Africa, in Mozambique and Zanzibar. The adults range from one to nearly two metres in length. Their markings, colourations and general characters are described, and there are excellent photographs of the snake and its fangs. It lives near water and edges of forests bordering on collections of water, and feeds on small rodents, birds, monkeys and frogs, and bites cattle coming to drink and natives if they disturb it. The symptoms in man may be very serious—local haemorrhage and oedema, sloughing, gangrene and neurotoxic effects. One to 3 cc. of venom may be obtained from the glands. A rabbit is killed by the venom in 2–4 hours, after a period of dyspnoea and incoordination, and, *post mortem*, massive and generalized haemorrhages are seen. Injected subcutaneously, the venom is less toxic than that of *B. arietans*, but, intravenously, the opposite holds. When the venom of *B. gabonica* was added to blood from a case of haemophilia, by addition of 1/10,000 of the volume of blood, the coagulation time was reduced, from 25 minutes to 5–6 minutes; in another case, from 32 to 11 minutes, whereas that of *B. arietans* had no effect. It was observed, however, that different specimens of *B. gabonica* venom varied considerably in haemostatic power.

Antivenenes were prepared by injection of increasing doses of *B. gabonica* anavenene, obtained by adding 0·75 per cent. formol to 1 per cent. venom, and keeping the mixture at 37°C. for 6 weeks, into the horse. The antivenene was effective against *B. arietans* venom, but the reverse did not hold good—*B. arietans* antivenene was ineffectual against the venom of *B. gabonica*. It can be concentrated to one-fourth or one-sixth. One cc. of the concentrated antivenene will neutralize 20 mgm. of the dried venom and 1 cc. of the original venom may be taken as an average amount injected at a bite (equalling 200 mgm. dried venom), so an ampoule of 10 cc. will usually suffice; but as a large snake may inject as much as 3 cc., two or even three ampoules may have to be given to be on the safe side. *H. Harold Scott.*

BOQUET, P. Sur l'action dépressive du venin de *Bitis arietans*. [**The (Cardiac) Depressive Effect of the Venom of** *Bitis arietans*.] *Ann. Inst. Pasteur.* 1946, May–June, v. 72, Nos. 5/6, 478–80, 1 fig.

ESSEX and MARKOWITZ showed as long ago as 1930 that *Crotalus* venom had an effect analogous to that of injection of histamine, and later CHOPRA and CHOWAN, and KELLAWAY and his co-workers, put forward the hypothesis that the venom produces histamine substances in the body, with effects comparable with anaphylactic shock and fall of blood-pressure.

If 2 mgm. of the venom of *Bitis arietans* be injected intravenously into a rabbit weighing 2 kilogrammes, death ensues in a few hours; 0·4 mgm. is not fatal but causes rapid and marked fall in the carotid pressure. A tracing in this communication shows this very clearly. The animal recovers from this in 10–15 minutes. With larger doses, 0·4–1·0 mgm. per kilo, the effects are more intense and more lasting. Two non-fatal doses injected at 15 minutes' interval result in a prolonged reduction of arterial pressure, and desensitize the

animal against the depressant effect of a third dose a quarter of an hour later. But, whereas the depression resulting from histamine is abrogated by administration of an anaesthetic, this is not so in the case of the venom of *B. arietans*; the analogy, therefore, with histamine is not complete. *H. Harold Scott.*

CROXATTO, H. **Hypertensinase Activity of an L-Aminoacid Oxidase Preparation and of the Venom of** *Bothrops neuwiidi*. *Proc. Soc. Exper. Biol. & Med.* 1946, June, v. 62, No. 2, 146–8.

ERRATUM.

In the abstract of the paper by GRASSET, SCHAAFSMA and HODGSON, this *Bulletin*, 1946, v. 43, 671, line 2, the dose of venom of *Hadogenes*, needed to kill a guineapig, when injected subcutaneously, is given as 185 gm. This should read 185 mgm.—*Ed.*

DERMATOLOGY AND FUNGUS DISEASES.

ROSENTHAL, J. **Atypical Lichen Planus.** *Amer. J. Path.* 1946, May, v. 22, No. 3, 473–91, 4 figs. on 1 pl.

Several papers concerning the clinical signs and symptoms of tropical lichen planus have been published [this *Bulletin*, 1946, v. 43, 149; 479: also *Bulletin* of *War Medicine*, 1946, v. 6, 333] but this is one of the first concerning the pathology of the disease.

Rosenthal's paper is divided into three sections: the first concerns the histology of 21 specimens of biopsy material; the second, the haematological analyses of 18 cases; the third, results of autopsy of an adult white male who died while suffering from the malady.

Atypical lichen planus has several clinical manifestations, which range from lichenoid eruptions of varying severity to generalized exfoliation; nevertheless, on a morphological basis, Rosenthal has been able roughly to classify the histological findings into three stages, which he terms acute, subacute, chronic or healing, but these merge, so that occasionally the central area of a section indicates one stage of the disease while the periphery has a different appearance. Of the 21 specimens examined, 6 showed the acute phase, 7 the subacute, and 8 the chronic or healing stage.

"The acute stage is marked principally by an acute inflammatory exudate, limited to the papillary and subpapillary connective tissue, which extends along the hair shafts, and consists of large numbers of lymphocytes and histiocytes. There is marked acanthosis and hyperkeratinization with plugging of the openings of the hair follicles. The stratum basalis [*sic*] is edematous, liquefied, and infiltrated with large numbers of inflammatory cells, mostly lymphocytes and histiocytes. Large collections of pigment are frequently found at the tips of the papillae. Such collections may also be found in the subpapillary layers. The subcutaneous tissue is not involved."

"The inflammatory reaction is still apparent in the subacute stage, but to a much lesser degree. Inflammatory cells in moderate numbers are still present. The outstanding lesion is the degenerative change in the stratum basalis with resultant atrophy and sharpening of the rete pegs. Considerable edema is present both in the lower epidermis and in the corium. Collections of pigment are frequently seen in the papillary or subpapillary connective tissue."

"The inflammatory reaction has largely subsided in the chronic stage. Sufficient residua are present, however, to indicate the origin of the lesion.

Scattered inflammatory cells as well as occasional small foci are still present in the upper layers of the corium. Some restitution has occurred in the basal layer and some of the rete pegs are of usual width and appearance. Others, however, show persistent degenerative changes in the basal layer with consequent sharpening of their outlines. Small masses of pigment are occasionally seen in the papillary and subpapillary connective tissue. When seen in this stage, it is extremely difficult to differentiate this condition from other toxic dermatoses in tissue sections."

Certain histological changes are common to the three stages; these include thickening of the horny layer, blocking of the follicular orifices by keratin plugs, and degenerative and liquefactive changes in the cells of the basal layer of the epidermis. Spongiosis often occurs. Usually there is an increase of pigment in the basal layer. A cellular infiltrate which varies with the severity of the disease, and which chiefly consists of lymphocytes and histiocytes, is present in the papillary and subpapillary layers of the corium, and tends to cluster round hair shafts, hair follicles, and glandular tissues. Also aggregations of pigment can be noted—particularly in acute cases—in the two upper layers of the corium, and most characteristically at the tips of the papillae. The pigment is a melanin, and most of it is enclosed in macrophages, although some may be scattered in the stroma.

Rosenthal gives full reports concerning blood examinations which were made in 18 cases. A moderate anaemia was found in 12 of these, but in one case the red cell count was as low as 980,000, and the haemoglobin 20 per cent. Lymphocytosis and slight degrees of eosinophilia occurred in some 70 per cent. of the cases. Occasionally biochemical changes were noted in the blood; these consisted in a decrease of the total protein and a lowering of the albumin-globulin ratio, but the author carefully states that as biochemical examinations were made only in the more severe cases, the figures which he gives are not representative for the whole series. In a complete statistical study of unselected cases, the figures would undoubtedly be different. Two patients had severe haemopoietic disturbance, and one of these died. A blood culture after death revealed the presence of haemolytic staphylococci and streptococci. A full account of the post-mortem findings is given, and the full diagnoses are summarized thus:—

"(1) Lichen planus (New Guinea); (2) aplastic anemia; (3) focal myocardial hemorrhages and necrosis; (4) bilateral pleural effusion; (5) pulmonary edema; (6) congestion of spleen; (7) hepatitis, subacute; (8) bilateral pelvic hemorrhages in kidneys; (9) subarachnoid and intraventricular hemorrhages; (10) hypoplasia and fatty change of bone marrow; (11) multiple ecchymoses of skin, voluntary muscles, diaphragm, and viscera."

The lesions found in the liver were regarded as being of special interest: they consisted in subacute hepatitis, characterized by degeneration of liver tissue and accumulation of chronic inflammatory cells. "In addition, isolated masses of pigment were found which were iron-negative and melanin-positive (Becker stain). The Kupffer cells also contained large amounts of pigment. It is assumed that this pigment is bile pigment. However there is some resemblance to the melanin pigment of the skin.

"With ultraviolet light the liver showed a marked greenish fluorescence. The presence of this marked fluorescence in a pathologic liver of a patient who had not had atabrine [mepacrine] for 6 weeks prior to his death again called attention to the possibility of atabrine being a factor in this disease. Since, however, this is the only case that I have seen, no definite conclusions are warranted."

The author concludes by stating: "It still is not clear why this condition should occur proportionately much more frequently in New Guinea than other

regions where similar conditions prevail. It is possible that atabrine is only one of the factors in a chain of causes which may eventually be found in diet, climate, ingested drugs, insecticides, or infection with malaria."

R. M. B. MacKenna.

ERRECART, L. M. Sobre veinticinco casos de esporotricosis en el Departamento de Flores. [**Twenty-Five Cases of Sporotrichosis in Flores.**] *Arch. Uruguayos de Med., Cirug. y Especialidades.* 1946, Mar., v. 28, No. 3, 249–53. English summary.

"The author diagnosed twenty-seven cases of sporotrichosis during fourteen years. He thinks that sporotrichosis is a frequent disease not only in Flores but also in the other localities of Uruguay. No one lesion of the lungs was observed. Twenty-six cases were localized in the upper limbs and one in a leg. All patients were males."

HEAT STROKE AND ALLIED CONDITIONS.

MACKWORTH, N. H. **Effects of Heat on Wireless Telegraphy Operators Hearing and Recording Morse Messages.** *Brit. J. Indust. Med.* 1946, July, v. 3, No. 3, 143–58, 9 figs. [Summary appears also in *Bulletin of Hygiene.*]

The decline in the capacity for manual work caused by exposure to high air temperatures, especially in humid atmospheres, has long been recognized. It is a matter of common experience that one's inclination for mental effort may diminish in very hot environments, but the effects of heat on the capacity for mental work have not hitherto been clearly demonstrated experimentally. That is probably due to the experimental arrangements employed in some of the earlier investigations, for in those studies different types of tests were used during any particular work-spell, so that at intervals of 20 or 30 minutes there was a change of activity which introduced the powerful stimulus of variety. Many tasks are monotonous rather than variable, and to assess the influence of temperature on the performance of such tasks, protracted experiments are necessary. Such experiments were performed in the research described in this important paper, with the result that a diminished performance in very hot environments was clearly shown.

The research was carried out on behalf of the Medical Research Council's Royal Naval Personnel Research Committee. That Committee wanted to know whether high temperatures affected some forms of human activity more than others, so that it could be ascertained whether certain compartments in H.M. ships should have priority in the allocation of air-conditioning equipment; and, further, it was desired to learn the extent of the overlap between the physiological effects of heat and the effects of heat on human performance as measured by psychological experiment.

In the study here reported the performance of eleven physically fit wireless telegraphy operators was examined. Before the main tests they were acclimatized by exposure to effective temperatures of 87·5°F. to 97°F. for three hours a day, five or six days a week, over a period of seven to eleven weeks. On the test days work was done for three hours, during which period nine messages, each of 250 groups, were transmitted at a speed of 22 words per minute. That is to say, messages were transmitted for about 16 minutes, with 3-minute intervals between messages.

The wind velocity was 100 ft. per min. throughout the series of tests, the dry-bulb temperature on different days was 85°, 90°, 95°, 100°, or 105°F., and in each instance the wet-bulb was 10°F. below the dry-bulb temperature. These conditions represented effective temperatures of 79°, 83°, 87·5°, 92° and 97°F. Rectal temperatures were measured at the beginning and end of each work-spell. The men wore gym-shoes and white drill shorts, and wrote the morse messages while seated at a table. There was plenty of unsalted water for drinking, and each had a daily ration of 10 gm. of salt in addition to the ordinary dietary intake. During the run of the experiments the men had no exact knowledge of the accuracy of their performance on a particular day.

The main conclusions drawn from this investigation are :—

1. Hot and moist atmospheres seriously impaired the accuracy with which these trained men could record morse messages heard over their headphones.
2. A statistically significant reduction in their accuracy first appeared when they were exposed to an effective temperature of 87·5°F. (with 95°F. dry-bulb and 85° wet-bulb temperature). It had earlier been observed that most wireless telegraphy ratings in the Eastern Fleet had to work at effective temperatures of more than 84°F., and that conditions were worse during prolonged spells at action stations.
3. Hot and moist atmospheres raised the rectal temperatures.
4. Rectal temperature did not give even an approximate idea of the accuracy of work at wireless telegraphy reception.
5. Hence, raised body temperature did not cause deterioration in ability to receive wireless signals, within the range of atmospheric conditions encountered by ratings in the Eastern Fleet.

It was noteworthy that the exceptionally competent members of the group were less affected by the difficult atmospheric conditions than men regarded as very good operators. Men of ordinary ability showed the greatest deterioration of all. [This is an interesting point. Other studies of industrial fatigue have shown that the more competent workers show less sign of fatigue than their fellows.]

There were no signs of cumulative effects from day to day, but during a 3-hour spell the number of errors per hour rose progressively. Commonly, errors were twice as numerous in the second hour as in the first, and three or four times as numerous in the third hour. Severe head colds increased the rate of this falling-off in accuracy. *Thomas Bedford.*

MISCELLANEOUS DISEASES.

MANSON-BAHR, P. **Some Tropical Diseases in General Practice. "A Post-War Legacy."** *Glasgow Med. J.* 1946, May, v. 27, No. 5, 123–30.

In this lecture Sir Philip Manson-Bahr reviews briefly the experience of certain tropical diseases as they affected the troops in the recent war and its predecessor, and as they may affect practitioners in Britain who are faced with the difficult questions of diagnosis and treatment of these cases of, to them, uncommon and baffling complaints. He brings the experience of a lifetime to the evaluation of the important features, noting that problems now sometimes regarded as new are, in fact, repetitions of those which arose 30 years ago. The sequelae of amoebiasis, for instance, are rightly regarded seriously, but after the war of 1914–18 it was found that the disease gradually " petered out ", and no doubt this will happen again ; in the meantime, effective treatment is by no means impossible, and it is important to avoid the amoebiasis neurosis.

Malaria has been controlled, during the war, more effectively than ever before, and treatment is now very good. Although it is a correct attitude of mind to think first of malaria in soldiers who return from the East, a too facile diagnosis of enlarged spleen as due to malaria may lead to serious errors ; " the enlarged spleen usually retracts and disappears after one year's residence in a temperate climate ", and in such patients some other cause should first be sought.

Sprue is still a mystery ; the author favours the view that it is due to some infective agent. In treatment, careful dieting and nursing are needed, but injections of crude liver extract are very useful. *Charles Wilcocks.*

McCoy, O. R. **Precautions by the Army to prevent the Introduction of Tropical Diseases.** *Amer. J. Trop. Med.* 1946, May, v. 26, No. 3, 351–5.

In this address to the Annual Meeting of the American Society of Tropical Medicine in November 1945, Colonel McCoy considers the problems arising from the return of troops from tropical theatres of operation to the United States.

He begins by pointing out that high standards of preventive medicine have been enforced among troops overseas, and that troops in endemic areas have been immunized against such infections as yellow fever, cholera and plague.

Malaria has been the greatest disease problem and the author reveals that between December 1941 and June 1945 there were 430,000 hospital admissions for malaria in the U.S. Army.

Steps taken to minimize the hazards of malaria recurring when soldiers return to the United States include a co-ordinated mosquito control organization, continued suppressive medication for 28 days after arrival in the United States, and examination of the man and his blood before demobilization, if conditions indicate it.

Colonel McCoy goes on to discuss the problems of dysentery, dengue, sand-fly fever and scrub typhus. The hazard from dengue is the greatest, and stringent *Aëdes* control is essential at Army bases and airports. The possibility of the introduction of *Ancylostoma duodenale* is discussed. This species presents a greater problem than *Necator americanus*, because it is more harmful, more resistant to climatic conditions and less amenable to treatment. Other helminthic diseases are also mentioned. General quarantine measures have been improved and strengthened, and a joint Army, Navy and Public Health Service Quarantine Board has been set up ; and this Board takes advantage of the facilities for immunization and supervision exercised over members of the Forces.

The problems and the measures designed to deal with them are on orthodox lines, and the paper contains little that is original for the British reader. The relative urgency of the problem is underlined by two local factors ; firstly, that American citizens have been spread over a larger area of the tropics, and exposed to greater hazards of disease which is indigenous there, than ever before in their history ; secondly, that conditions in certain parts of their vast Continent are favourable to the maintenance and dissemination of some tropical diseases which would not flourish in more evenly temperate climates. The urgency is therefore more obtrusive to United States health legislators than to our own. *H. J. O'D. Burke-Gaffney.*

Trenchard, H. J. **Inability to work in a Tropical Climate.** *Brit. Med. J.* 1946, Sept. 21, 416–18.

This paper discusses the factors in invaliding between October 1944 and September 1945, 373 Royal Air Force men, chiefly ground staff, found unfit for

duty in South East Asia, although not necessarily unfit for further military service in the United Kingdom.

The age of the men varied from 18 to 47, the majority being between 20 and 30. Most had been in the R.A.F. between two and five years, and their service overseas varied from 2 to 51 months; the incidence of invaliding, excluding that due to tropical diseases, showed peaks during the first twelve months and after eighteen months of service overseas.

The principal causes of invaliding were:—injuries 50; organic diseases, excluding pulmonary tuberculosis which was not dealt with at this centre, 176; and psychological abnormalities 147. The majority of the invalided were fit enough to travel by normal trooping arrangements, only 60, of whom 18 had injuries, requiring transport by hospital ship.

Of the surgical cases the injuries formed an important proportion, although only five were directly due to enemy action, while of the surgical diseases, disorders of the urinary system, particularly calculus, were noteworthy.

There were 50 patients with skin diseases, of whom 10 had trouble before going overseas, and the commonest conditions were epidermophytosis 12, and seborrhoeic dermatitis 12.

Tropical diseases accounted for 59 invalidings, of which 34 were due to sprue and 15 to amoebiasis; only 2 patients were invalided with malaria, a low figure, thought to be due to the efficiency of mepacrine suppression. The main causes for repatriation in amoebiasis were amoebic hepatitis, persistent relapses of bowel infection, and the development of a "pre-sprue type of condition."

Of psychological abnormalities, anxiety state was diagnosed in 86 patient s hysteria in 33, psychoses, mostly schizophrenia, in 15, and psychopathic personality in 11. The principal precipitating factors of the anxiety neuroses appeared to be family or financial worries, infidelity of the wife, or discomforts of overseas service, but in 15 cases no outstanding factor could be discovered. In those suffering from hysteria, the precipitating cause appeared to be a subconscious desire to return home, while the principal symptoms were headaches, depression, dizziness or dyspepsia. A feature of the psychotic patients and those diagnosed as being of psychopathic personality, was the length of time that they were able to serve overseas before requiring invaliding, some carrying on for more than two years. *F. Murgatroyd.*

HEILIG, R. **Some Advances in Medical Treatment.** *J. Indian Med. Ass.* 1946, June, v. 15, No. 9, 308–12. [38 refs.]

This is a succinct but useful review, in which modern work on the sulphonamides, penicillin, streptomycin, prostigmine, nicotinic acid, pyridoxine, thiouracil and the anti-malarial drugs is summarized. Sulphadiazine has almost supplanted the other compounds of the series, and the author, noting its efficacy in bacillary dysentery, remarks that there is no reason why it should not be equally effective in cholera. He gives concise information on the use of penicillin in gonorrhoea, according to the most recent work available. The story of the Australian work on mepacrine and Paludrine is briefly recounted.
Charles Wilcocks.

FEIGENBAUM, A. & KORNBLUETH, W. **Behcet's Disease as Manifestation of a Chronic Septic Condition connected with a Constitutional Disorder. With a Report of Four Cases.** *Acta Med. Orientalia* (*Palestine & Near East Med. J.*). 1946, May, v. 5, No. 5, 139–51. [Numerous refs.]

The authors present a very clear account of this peculiar disease, which is characterized by ulcers in the mouth and on the genitalia, with eye lesions—

hypopyon, irido-cyclitis, retinitis, optic neuritis—and by an eruption like that of erythema nodosum. Though cases have been reported from time to time since the end of the last century, little, if anything, is known concerning the aetiology or pathogeny, and treatment is far from satisfactory. Sometimes one or more of the symptoms mentioned above is absent. Partial cure seems to occur spontaneously in some cases, but relapses come on after intervals of varying length, perhaps 6–7 years.

Four cases are detailed in this paper, three males of 24, 25 and 28 years, and one female of 25 years. One man died with nervous symptoms, headache, dizziness and convulsions, the woman left hospital and could not be traced; two improved. *Staphylococcus aureus* was cultivated from the lesions and the syndrome is thought to be due to a chronic septic condition in persons predisposed by, in most cases, latent tuberculosis, trauma playing a part and possibly a large part, in the primary localization of lesions. Though improvement in the general health takes place in non-fatal cases, it will be obvious from the severity of the eye symptoms that the damage to the sight may be great and permanent. Treatment by sulphonamides and penicillin and by injection of autogenous vaccines has been tried, in some with apparent benefit, but it is thought that the dosage may have been inadequate. The authors have given a helpful review of the literature of the subject and a very full list (two complete pages) of references to this interesting condition. [See also this *Bulletin*, 1944, v. 41, 780; 1946, v. 43, 157.] *H. Harold Scott.*

Rao, V. G. **Some Observations on Cases of Ascites in Hyderabad-Deccan.** *J. Indian Med. Ass.* 1946, May & June, v. 15, Nos. 8 & 9, 254–62; 295–300. [59 refs.]

Among 343 consecutive cases of ascites admitted to the Osmania Hospital in two years, there were 52 in which no definite organic disease was detected, these are classed as being due to "nutritional deficiency". Most of the 52 were young or middle-aged adults of the labouring class, whose diet provides sufficient calories, but is of poor quality and deficient in protein. Although there were approximately equal numbers of the two sexes in the general admissions to hospital, 46 of these 52 cases of "nutritional ascites" occurred in males. In some patients the ascites was accompanied by pleural and pericardial effusions, and by anaemia of moderate degree. Serum proteins were determined in 8 patients, in 7 of whom the ratio of globulin to albumin was greater than 1.

The majority of the patients recovered with rest in hospital and on a diet more liberal and better balanced than that at home. Complete disappearance of the ascites, followed by gain in real weight, was obtained in 32 cases, and the condition of 10 others was improved. Seven patients died.

Only a few patients were followed up after leaving hospital; 15 were known to be in good health for periods varying up to 2 years. Four patients who were classed as having "nutritional ascites", and who were discharged after clinical recovery, returned later; two with cirrhosis of the liver, one with pulmonary tuberculosis, and one with pleurisy.

The second part of this paper records the findings in the 108 cases of portal cirrhosis included in the 343 cases of ascites. The condition appears to be common in India, but, apart from a suggestion that defective diets play some part, there is no evidence to explain its etiology. Twenty of the 108 patients were vegetarians and total abstainers because of their religion, and from only 40 of the remainder could a history of occasional "toddy" or "sendhi" drinking be obtained. (The alcoholic content of these drinks is only about 7 per cent.)

Bleeding was uncommon in these patients ; only one had haematemesis, three had melaena,and five had bleeding piles. Examination of a few cases showed moderate anaemia, and low serum proteins with a reversed albumin/globulin ratio. Response to treatment was unsatisfactory, and, unlike the patients with " nutritional ascites ", many of the patients died in hospital, while most of the remainder showed little improvement after repeated paracenteses.

It is suggested that cases classed as " nutritional ascites " may at first be due to simple malnutrition without gross hepatic lesions, and may be capable of recovery, but that a continued state of malnutrition may ultimately result in a fully developed picture of portal cirrhosis. *H. E. Harding.*

BECKER, B. J. P. **Cardio-Vascular Disease in the Bantu and Coloured Races of South Africa. I. Incidence, Pathology and General Features.** *South African J. Med. Sci.* 1946, Apr., v. 11, No. 1, 1–14, 3 figs. [13 refs.] **II. Congenital Heart Disease.** *Ibid.* 15–17. [10 refs.] **III. Rheumatic Heart Disease.** *Ibid.* 18–34, 1 fig. [43 refs.]

These three papers, or sections of one contribution, are excerpts from a doctorate thesis. They comprise an analysis of those among 3,000 autopsies performed at the Johannesburg General Hospital during 14½ years ending June, 1938, showing cardiac or cardio-vascular disease. Some 12 per cent. of Bantus and coloured persons were found to have died from circulatory disease, a proportion about the same as that recorded in other parts of the world.

For the purpose of his analysis the author uses the following classification : Congenital, and Acquired, 2·5 and 97·5 per cent. respectively, and the latter he subdivides into three main groups : Inflammatory which includes rheumatic, syphilitic and tuberculous ; Metabolic and Physical which includes atheroma, arteriosclerosis and beriberi ; and, thirdly, Neoplastic—a classification not altogether satisfying.

Among the 3,000 there were 1,385, or 46 per cent., showing some disease of the circulatory system. As regards sex, 1,041 occurred among 2,190 males autopsied (47·5 per cent.) and 344 among 810 females (42·5 per cent.), so that sex differences are negligible. No indication was found of any special racial susceptibility among the seven races making up the total.

Atheroma was the commonest lesion found and, next to this, hypertensive heart disease, but in the majority these were not the sole lesions. Tuberculous disease of the heart was found in 4 per cent. of those dying under 30 years of age and in 8 per cent. of those over 30 years ; syphilitic disease was less in evidence, in only 2 per cent. below 30 years, and in 9 per cent. of those over 30 years.

As regards valvular lesions, there were 106 cases of aortic incompetence among the 3,000 autopsies (3·5 per cent.), 57 (1·9) of mitral stenosis, 16 (0·5) of aortic stenosis, and 5 (0·2) of mitral incompetence. There were 51 cases of aneurysm, most due to syphilitic aortitis, and 37 of the patients died from rupture of them.

In the second paper, the author records that there were 35 cases of congenital heart disease among the 3,000 (1·16 per cent.) ; excluding abnormalities of the vessels, hypoplasia and aneurysm, and displacement due to primary diaphragmatic deficiency, this figure is reduced to 13 (0·4 per cent.). Infective endocarditis was found in two only of these congenital cases.

In the third paper, rheumatic heart disease is discussed in more detail. One hundred and six such (3·5 per cent.) were found among the 3,000. It was most common in the 11–20-year group, constituting 10 per cent. of the autopsies and 33·7 per cent. of the cardiac cases. Among females with organic heart disease " rheumatic heart " was present in 15 per cent., among males 5 per cent. ; but the variation in females is stated to be 5·5–24·5 per cent. and in

males 1·5–8·5. " There is thus ", says the author, " no significant difference " [a conclusion not easy to follow]. For this analysis the author classifies rheumatic heart disease into three main groups : Acute rheumatic carditis, latent (developing) carditis, and developed lesions. These are, each of them, further sub-divided and discussed. Space forbids more detailed account here ; those interested should consult the original paper, or, better still, the complete thesis if it is published. Suffice it here to say that the mitral valve was involved alone in 38, and together with other lesions in 42, or 80 in all. The aortic valve alone was involved in 23. In about one-third of the cases of rheumatic heart disease bacterial endocarditis was superimposed ; the aortic valve was affected in this way more often than the mitral, and both together in four. Among the author's conclusions two are particularly striking. First, " In its age and sex incidence among Bantu and Coloured races, it [rheumatic heart disease] cannot be said to differ in any essential way from the condition as seen in other parts of the world " ; secondly, " There is a somewhat higher incidence of bacterial endocarditis in Bantu and Coloured subjects in association with rheumatic valvulitis than occurs in other parts of the world." [The whole is an interesting and painstaking study.] *H. Harold Scott.*

D'Arcangelo, D. Le cardiopatie nei nativi dell'Eritrea. (Considerazioni eziopatogenetiche, cliniche, statistiche.) [**Heart Disease in Eritreans.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1945, v. 5, Nos. 5/6, 231–46. [42 refs.] English summary (4 lines).

Stephan, E. **Tropical Eosinophilia in Egypt. Report of a Case.** *Lancet.* 1946, Aug. 17, 236.

Goldstein, B. **Two Cases of Disseminated Sclerosis in African Natives.** *East African Med. J.* 1946, June, v. 23, No. 6, 170–73.

Buffa, F. & d'Arcangelo, D. Sui casi di cancro del laringe osservati in Eritrea (contributo clinico-statistico). [**On Cases of Cancer of the Larynx in Eritrea.**] *Bull. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1945, v. 5, Nos. 5/6, 135–49. [24 refs.] English summary (4 lines).

GENERAL ENTOMOLOGY.

Tshinaev, P. P. [**Flying Activity and Attack on Man of Various Species of *Anopheles* and Culicines under Natural Conditions in Uzbekistan.**] *Med. Parasit. & Parasitic Dis.* Moscow. 1945, v. 14, No. 5, 15–35, 11 figs. [In Russian.]

The author records the results of observations upon the flying activity and attacks upon man of mosquitoes, carried out chiefly among the rice-fields of Uzbekistan, from March to October of the years 1939–1943. The study was restricted to *Anopheles* and Culicines (*Anopheles maculipennis sacharovi, A. hyrcanus, A. claviger* (*bifurcatus*), *A. superpictus, A. pulcherrimus* ; *Uranotaenia* ; *Theobaldia longiareolata, T. annulata* ; *Mansonia* ; *Aëdes caspius, Aëdes detritus, Aëdes pulchritarsis, Aëdes vexans* ; *Culex*).

Counts were made by using a trap constructed as follows : a sheet was suspended on four poles, with the edges touching the ground, one side of the sheet being raised during the observations, to form an inlet for the mosquitoes. One or two men, who served to attract the insects and remained under cover of

this tent, with a lamp burning all night, made observations on and collected the mosquitoes, keeping hourly records of temperature, humidity and wind. When flight ceased, the sheet was removed.

The results shown in numerous tables and charts were as follows : among the Anopheline and Culicine mosquitoes, entering the tent, unfed females formed 87 per cent. ; those with blood in the stomach 8·4 per cent. ; those with developed ovaries 2·3 per cent. ; males were 1·7 per cent. The maximum number of attacking mosquitoes was observed in July, constituting 38·2 per cent. of a total number of actively attacking mosquitoes during the whole season. The minimum density was in April (1·5 per cent.), in May (2·6 per cent.), and in October (3·1 per cent.). The temperature limit at which activity was highest was 33·5°C., while at 9°C. it was lowest, the temperatures being between 15° and 28°C. in May, and 11°–15° in October, with intermediate values in September and April. As regards humidity, it was found that 100 per cent. relative humidity had a depressing effect upon the activity of mosquitoes. The insects manifested a positive phototaxis to the weak source of artificial illumination, while sunlight at temperatures not exceeding 20°C. had no inhibiting effect. However, high temperatures combined with intensive insolation and evaporation were unfavourable, the mosquitoes keeping to their day-shelters under these conditions. The mechanical and desiccating action of wind proved to be of primary importance. The maximum speed of wind at which flight of mosquitoes took place was 4·17 metres per second ; when the speed does not exceed 2 m/sec. they fly in the open air ; above this speed they fly low, in the grass. The daily rhythm in the attacks of mosquitoes corresponds to periods of evening and morning maxima, and night and afternoon minima of flying activity. During the maximum evening periods, the first mosquitoes to attack are *Aëdes caspius* and *Culex*, the density of which increases progressively from sunset to night, after which it declines, while the density of *Anopheles* begins to rise. *C. A. Hoare.*

Mara, L. Considerazioni sul rinvenimento dell' *Aedes aegypti* L. (*Dip. aedinae*) ad altitudini d'eccezione e brevi note sulla fauna culicidica del M. Bizen (Eritrea, A. O.). [**A Note on the Finding of *Aëdes aegypti* at an exceptional Altitude with a Short Note on the Culicide Fauna of Mt. Bizen.**] *Boll. Soc. Ital. di Med. e Igiene Trop.* (Sez. Eritrea). 1945, v. 5, Nos. 5/6, 189–98. [16 refs.] English summary.

" In this note it is said that *Aëdes aegypti* L. has been found on the Bizen mountain (Eritrea, East Africa), at the exceptional altitude of 2,400 metres above sea level. This altitude is 450 metres higher than that previously quoted by other authors in Kenya Colony (1,950 metres above sea level)."

Wisecup, C. B., Brothers, W. C., Eide, P. M. & Deonier, C. C. **DDT Emulsion applied to Rice-Field Water to control Mosquitoes.** *J. Econom. Entom.* 1946, Feb., v. 39, No. 1, 52–5.

The authors' object was to run DDT emulsion into irrigation water in the channel before it flowed on to the rice field, thus attaining distribution through the mechanical flow of the water. The stock concentrate consisted of 20 per cent. of DDT, 20 per cent. of *Triton X-100*, a proprietary emulsifier, and 60 per cent. of xylene ; this was diluted with water, before application by means of a drip can.

Concentrations of DDT of less than 0·1 part per million gave very limited control. Doses of 0·2 p.p.m. and 0·4 p.p.m. gave control of breeding in fields near to the channels on which the treatment was applied, but not in the more

distant fields. A dose of 0·6 p.p.m. gave complete initial control, and residual control was noted in some cases. It is concluded that the degree of control depended on : (*a*) the concentration of the DDT emulsion in the water ; (*b*) the dosage of DDT per acre ; (*c*) the distance that the emulsion was carried in the channel before it entered the field ; and (*d*) the size of the field. Subsequent laboratory tests have shown that intense aeration of water containing DDT causes a decided loss of toxicity to mosquito larvae.

There was no noticeable damage to the rice, and no decrease of plump grains, in the treated fields. The mosquitoes concerned were *Anopheles* and *Psorophora*.

G. Macdonald.

California Mosquito Control Association. **Proceedings and Papers of the Fourteenth Annual Conference of the California Mosquito Control Association held at Agriculture Hall, University of California, February 25 & February 26, 1946.** 115 mimeographed pp., 2 figs. [$1.50]

This is an account, in 115 pages, of a conference of the California Mosquito Control Association, held in Berkeley, California, in February 1946.

It includes 19 technical papers and 3 reports on field work in different districts, and covers a wide range of material, largely concerning the use of DDT in malaria control. There is a full account of the discussions which took place during the Conference.

To appreciate the background of this Conference and the significance of the subjects discussed, the original *Proceedings* should be studied.

H. J. O'D. Burke-Gaffney.

Jayewickreme, S. H. & Niles, W. J. **Successful Feeding Experiments with an Adult Trombiculid Mite (Order Acarina).** [Correspondence.] *Nature.* 1946, June 29, 878.

Although nearly all workers interested in scrub typhus have tried to breed the trombiculid mites which are believed to transmit the rickettsia, little success has previously been achieved. We know that the larval stage must feed on a vertebrate host (*viz.* a rat) but the nymph and adult, living in the soil, have given more difficulty, and their food has not been recognized. A few have on occasion been reared in various media, but it has been obvious that the proper diet has not been discovered. Miyajima and Okumura state that *Trombicula akamushi* lives on plant juices, but other workers have not confirmed this.

The authors of this communication have, for the first time, discovered a satisfactory diet for nymphs and adults. They found *Trombicula acuscutellaris* larvae parasitizing rats and bandicoots, and obtained adults and nymphs crawling on the vegetation choking a pond in which the mosquito *Mansonia uniformis* was breeding. The adult and nymphal mites were found to attack *Mansonia* eggs with avidity, and also to feed on *Anopheles* eggs. This mite is clearly carnivorous in its adult and nymphal stages. *Kenneth Mellanby.*

Wharton, G. W. & Carver, R. K. **Food of Nymphs and Adults of *Neoschöngastia indica* (Hirst 1915).** *Science.* 1946, July 26, 76–7.

This investigation was very similar to that described by Jayewickreme and Niles (above), but the mite *Neoschöngastia indica* was used. The adults and nymphs were found to feed readily on mosquito eggs and on other insect eggs. They were also noticed to be cannibalistic, so this species also is clearly carnivorous. *Kenneth Mellanby.*

WILLIAMS, R. W. **The Laboratory Rearing of the Tropical Rat Mite,** *Liponyssus bacoti* **(Hirst).** *J. Parasitology.* 1946, June, v. 32, No. 3, 252–6, 4 figs.

Work on the transmission of filarial worms in the laboratory has generally been difficult owing to the lack of a suitable arthropod vector. *Liponyssus bacoti*, the "tropical rat mite", is an intermediate host of the filariid *Litomosoides carinii*. This mite is common in the United States, and is easily reared in the laboratory. An artificial rats' nest is made by placing loam soil half an inch deep in a box, and a layer of straw above the soil. Rats (either cotton rats or ordinary albinos) in small cages are placed in the box over the straw and soil. The whole arrangement is then stood in a tray of water to prevent the mites from escaping. The soil and straw provide a suitable harbourage for the mites, and absorb the rats' urine, the production of which is kept at a minimum by giving no water to drink. A high humidity, over 70 per cent. (preferably 85–90 per cent.) is recommended [it must approach saturation among the soil and straw]. A room temperature of 21°C. gives good results [again the mites will be in a different, warmer, micro-climate]. The mites receive no special attention except to ensure that the straw does not become too damp. One such culture started with 32 mites, and in a fortnight numbered over 1,000. The female mites lay about 7 eggs after each blood meal; they feed approximately every second day. The eggs hatch in two days, to give a six-legged larva which moults without feeding in about 24 hours. Breeding is said to be so prolific that the host rats may die from anaemia. [*Liponyssus* might also be used in the laboratory for work on the transmission of murine typhus; it has been shown to be a vector of this rickettsia, in *Rev. Applied Entom.* Ser. B., 1932, v. 20, 49.] *Kenneth Mellanby.*

WHARTON, G. W. & HARDCASTLE, A. B. **The Genus** *Neoschöngastia* **(Acarinida: Trombiculidae) in the Western Pacific Area.** *J. Parasitology.* 1946, June, v. 32, No. 3, 286–322, 15 figs. [16 refs.]

"1. The genus *Neoschöngastia* Ewing, 1929 is redefined.

"2. A key to the species of *Neoschöngastia* found in the Pacific area is given.

"3. Eleven new species and one new subspecies of larval *Neoschöngastia* are described.

"4. Two nymphs of *Neoschöngastia* are described and a diagnosis of the genus on nymphal characters is given."

DELPY, L. P. Revision par des voies expérimentales du genre *Hyalomma* C. L. Koch 1844 (*Acarina, Ixodoidea, Ixodidae*). Note préliminaire. [**Experimental Review of the Genus** *Hyalomma.* **A Preliminary Note.**] *Arch. Inst. d'Hessarek.* Teheran. 1946, Jan., v. 2, No. 2, 61–93, 2 figs. & 1 folding pl. [21 refs.]

WELSH, J. H. & SCHALLEK, W. **Arthropod Nervous Systems: a Review of their Structure and Function.** *Physiol. Rev.* 1946, July, v. 26, No. 3, 447–78. [Numerous refs.]

LABORATORY PROCEDURES.

ROGERS, K. B. **Oil Sterilisation of Syringes.** *Lancet.* 1946, July 20, 87–8.

The need for scrupulous sterilization of syringes and needles has been widely discussed of recent years, and the need is heightened by the recognition of the possibility that non-sterile instruments may transmit infective hepatitis.

Sterilization by hot oil was advocated as long ago as 1921 by WRIGHT and COLEBROOK in their "Technique of the Teat and Capillary Glass Tube."

The author recommends that immediately after use, the syringe should be rinsed in water, and thus freed of blood. The needle is then removed and the syringe filled three to four times with liquid paraffin at 130° to 140°C., with a second's pause at each filling. The needle is replaced and the oil again sucked in and expelled. The sterile syringe is kept in place in a test-tube by means of a folded strip of plaster.

The method has the advantage of speed, and there is no risk of haemolysis. The heat of the oil should not exceed 150°C., as the cement holding the glass to the metal parts may melt. With larger syringes, the piston may jam, owing to cooling and contraction of the glass; but it moves freely again within five minutes. Syringes treated in this way are not sterile on the outside and are thus unsuitable for operating-theatre purposes, but are satisfactory for ordinary injections. Oil sterilization does not kill spores contained in dried blood.

The author describes five experiments in support of the oil sterilization method. Cultures of staphylococci, streptococci, *Bact. coli commune* and *M. tuberculosis* contained within syringes or in blood which has infected syringes, were sterilized by from one to four fillings of oil at 120° to 140°C. Syringe barrels and pistons containing dried blood infected with *Staph. aureus* were sterilized by two minutes' immersion in oil at 120°C.

Blood containing spores of *B. subtilis* was dried in syringes; the spores were not killed after 12 minutes in oil at 120°C.

[It is not quite clear why the spores of *B. subtilis* were not exposed to the higher temperature ranges before it was concluded that they were not killed by oil sterilization.] *H. J. O'D. Burke-Gaffney.*

LERNER, E. M. **A Rapid Gram Stain for Tissue.** *Arch. Pathology.* 1946, June, v. 41, No. 6, 674–5.

The author describes a modification of the Gram stain for the demonstration of bacteria in tissues, which, he claims, overcomes the complications of time, labour and inadequate differentiation inherent in the recognized modifications. The method requires less than five minutes of actual staining time and, it is claimed, gives excellent morphological detail. Bacteria stand out sharply and spore-bearing organisms are recognized readily.

Paraffin sections of Zenker-fixed tissues are heated at 56°C. for two to six hours. The actual staining is essentially that of the Gram method for bacterial smears, consisting of the conventional crystal violet iodine solution, acetone-alcohol, and 1 per cent. safranin as a counterstain. Detailed steps in staining are described in the original paper. *H. J. O'D. Burke-Gaffney.*

DUNN, R. C. **A Hemoglobin Stain for Histologic Use based on the Cyanol-Hemoglobin Reaction.** *Arch. Pathology.* 1946, June, v. 41, No. 6, 676–7.

A cyanol-peroxidase reaction is described, which has been found by the author to be highly specific for haemoglobin in paraffin sections of tissue fixed

in 4 per cent. solution of formaldehyde buffered to *p*H 7·0. The specificity and sensitivity of cyanol as a haemoglobin stain is equal to that of patent blue V in most instances. The actual staining time is about ten minutes. By this method, haemoglobin stains blue to bluish grey.

The technique of this method is described in detail.

H. J. O'D. Burke-Gaffney.

REPORTS, SURVEYS AND MISCELLANEOUS PAPERS.

International Labour Review. 1946, Mar.–Apr., v. 53, Nos. 3/4, 194–9.

Land Aspects of Labour Problems in Kenya.

In the Kikuyu territory of South Nyeri, Kenya, the population is increasing at the rate of 2 per cent. per annum. The actual amount of land available was no more than 3·35 acres per family in 1944, which would be reduced to 2·61 acres in 1955; this is insufficient for subsistence. Other land is therefore sought, largely by tenant farming, but for various reasons there is little inducement for the tenant farmer to conserve land from which he may be evicted at any time. To augment their income, men seek paid employment away from their homes, leaving their wives to carry out all home farming, and the collection of fuel, which often involves long trips and the carrying of loads sometimes more than 200 lb. in weight. These women are fast becoming mere drudges.

The solution of this problem lies in part in removing a large proportion of the population from the land, and creating a wage-earning group, which involves provision for the housing, not only of the men, but of their families, at the places of employment. The general land policy envisaged by the Government of Kenya aims to check soil erosion, to secure the proper use of water and timber resources and to encourage efficient agriculture. "It is on the general standard of living of the people, even more than on the development of production for export, that the economic progress of the colony as a whole must primarily depend." Co-operative farming cannot be undertaken without elaborate preparations—fencing, clearing, provision of water supplies and adequate housing. Moreover, financial help, technical guidance and control by Government are essential before the African adopts effective methods. The natural tendency is towards over-cropping, over-stocking with useless cattle, under-fertilization and failure to conserve the resources. The two important factors are soil-conservation and water supplies, and a scheme to deal with these matters has been approved in principle; this will cost £60,000 in the first year and £600,000 in ten years. It is, however, realized that greater sums than these will be needed, but it is also known that the effort and expenditure are essential to relieve the over-populated and over-stocked areas, and to develop the country so that its people may be healthy and prosperous.

[The effect of these conditions on health are obvious, and in Kenya, as in South Africa, it is evident that the interdependence of the various departments of government is appreciated. The story of the Anchau settlement in Nigeria is apposite in that many departments have collaborated to good purpose, and that a large measure of control is necessary to overcome ingrained habits of inefficient farming, which were of little importance when land was plentiful, but which are dangerous now.] *Charles Wilcocks.*

GALE, G. W. **Health Centre Practice, Promotive Health Services and the Development of the Health Centres Scheme.** *South African Med. J.* 1946, June 22, v. 20, No. 12, 326–30.

The Health Centre system has been adopted as part of the Government plan for improving the health and medical services in the Union of South Africa [see this *Bulletin*, 1946, v. 43, 498–501], and a centre has been in existence since 1940 at Polela, Natal [see this *Bulletin*, 1944, v. 41, 611 ; 1946, v. 43, 162]. The idea of Health Centre work is not merely to provide a service for those who attend because they are ill, but to study all persons in the area, in their homes and by inducing them to come periodically for examination. Both preventive and curative services are provided, but the Health Centres will gradually supplant the special clinics. The provision of this service will often, if not always, depend upon initiative exercised by voluntary agencies. At present there exist in the Union 8 of these centres ; 3 more are to be started in July 1946, and 9 others in October. Each has now one medical officer, one to three nursing sisters, and subsidiary staff, but eventually there will be, in each centre, two medical officers, a dental surgeon (part-time), and increased staff in general. The training of the staffs is being undertaken partly at the former military hospital at Springfield, Durban, and partly in Health Centres in and around Durban. In June 1946 there were 16 medical officers and 60 health assistants in training.

These Health Centres will not only conduct their day-to-day work on the lines indicated ; they will also be research centres, free to conduct experiments, to evolve new techniques, and to adapt themselves to varying needs. The practice of social medicine and the study of all factors which bear on health will be within their sphere, as is indicated by the paper by KARK and KARK to which reference has already been made [this *Bulletin*, 1946, v. 43, 162].

[This work is admirably conceived, and the future progress of these centres will be watched with the greatest interest.] *Charles Wilcocks.*

PALLEY, A. & BRUWER, T. **An Analysis of the Medical and Social Conditions of Native Children attending Groote Schuur Hospital Paediatric Out-Patient Department.** *South African Med. J.* 1946, June 22, v. 20, No. 12, 339–41.

The authors made an investigation into certain aspects of living conditions of 61 unselected African children who attended the paediatric out-patient department of the Groote-Schuur hospital. Most of them were under 2 years of age, and in most cases the father supported the children, though some fathers had deserted their families ; the parents were interested in the health of their infants, and, even under adverse conditions, were good parents. It seems probable that the infant mortality rate is much higher in these urban Africans than in the Europeans.

Only 42 of the children lived in brick houses, the rest lived in shacks ; 38 houses were fit for human habitation, the remainder not. In 34 instances the family (2–10 persons) occupied one room only, for living and sleeping. In 45 families the fathers, and in 13 the mothers, were employed while their children were ill ; the monthly income varied from nothing to more than £15 per month, most families receiving from £5 to £10. The authors comment that for a family to exist on less than £10 per month means gross poverty, yet 85 per cent. of these families did so. Rent was usually up to £2 per month, but in 10 families it was between £2 and £5 ; travel to work by train or bus was necessary for 36 bread-winners.

Of these children, no less than 21 were suffering from tuberculosis, and 17 from other respiratory infections ; this fact is significant when considered in relation to the housing conditions and overcrowding.

Two-thirds of the children did not return to the hospital after the first visit, probably because a second visit was not thought necessary by the parent, or because it would mean loss of a day's pay ; or for other reasons, including the long wait at hospital, the lack of tact on the part of officials and " being badgered around from department to department."

Two-thirds of the children subsisted on a diet exclusively, or almost exclusively, of carbohydrate.

The authors conclude that in these people parental care is very good, housing deplorable, and poverty great ; the health conditions of the children are associated with these factors and with the poor diet. " The Out-Patient Department is working as a bad medical machine and should be overhauled."

Charles Wilcocks.

Cluver, E. H., Jokl, E. & Rorich, P. R. **The Physique of American, Canadian, English and South African School Children.** *South African J. Med. Sci.* 1946, Apr., v. 11, No. 1, 45–9, 2 figs.

Piers, F. **Studies in Pigmentation.** *East African Med. J.* 1946, July, v. 23, No. 7, 210–18. [15 refs.]

Noble, B. G. **A Method for Continuous Parenteral Administration of Penicillin and other Drugs.** *Science.* 1946, June 28, 759, 1 fig.

The author has devised an apparatus for continuous parenteral administration of penicillin and other drugs which, it is claimed, eliminates the disadvantages associated with frequent uncomfortable injections.

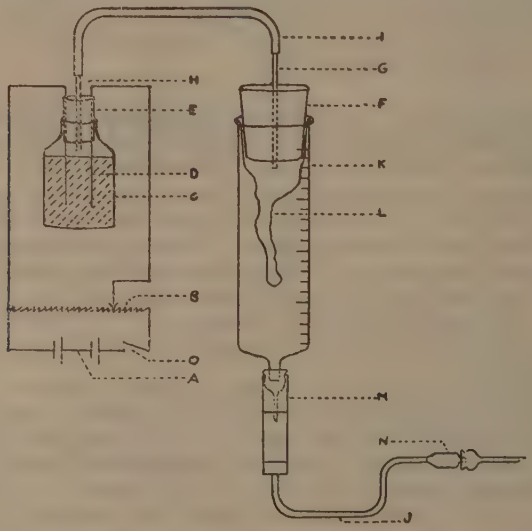

Fig. 1. A—two 1½-volt flashlight dry cells in series ; B—25,000-ohm potentiometer ; C—small electrolyte bottle of 3 per cent. KOH ; D—steel needle electrodes ; E, F—rubber stoppers ; G, H—hollow glass tubes ; I, J—small-lumen rubber tubing ; K—barrel of 20-cc. syringe ; L—rubber finger cot ; M—Murphy drip (size 23 needle inside a glass viewing tube) ; N—subcutaneous needle and adapter ; O—switch.

[Reproduced from *Science.*]

The basis of the apparatus is an inlaying, deep subcutaneous needle connected to a syringe with an automatic feed.

The apparatus consists of two flashlight batteries connected in series through a potentiometer with two steel electrodes, The electrolyte bottle, containing 3 per cent. KOH, is connected by rubber tubing with a rubber finger-cot in the syringe. Formation of gas expands the cot, forcing the contents from the syringe. The injection rate can be varied from 1 cc. per minute to 1 cc. per hour and is controlled by the potentiometer.

For use, 100,000 units of penicillin are loaded into the syringe (after solution in 20 cc. of normal saline) and the potentiometer adjusted to the desired rate of flow, indicated by an improvised Murphy drip.

The original model is compact and can be strapped to the leg or an arm- board. Battery drain is negligible.

Continuous injection for 10 to 12 hours caused little discomfort, other than a moderate fleeting tenderness. The only reaction observed was a local irritation which was probably due to too rapid injection. The injection rate should be slow enough for almost immediate absorption, with minimum subcutaneous collection of fluid. The apparatus can also be used for constant intravenous injections.

The apparatus is clearly explained in the accompanying diagram.

H. J. O'D. Burke-Gaffney.

BOOK REVIEWS.

Chandler, Asa C. [M.S., Ph.D., Professor of Biology, Rice Institute, Houston, Texas, etc.]. **Introduction to Parasitology with special reference to the Parasites of Man.** 7th Edition, pp. x + 716, 309 figs. 1944. New York : John Wiley & Sons, Inc. London : Chapman & Hall, Ltd. [30*s.*]

The appearance of a seventh edition of this well-known book will be welcomed not only by parasitologists but also by many others requiring a book about parasitology which is both sound and readable, yet presents the main principles and facts of this important branch of economic biology without obscuring them with too much detail. It is now 26 years since Chandler, rightly believing that scientific work flourishes best when it is supported by public opinion, tried to awaken public interest in parasitology by producing his *Animal Parasites and Human Disease.* This book was intended for the general public, but it was accepted more widely by American schools and universities as an introduction to parasitology. At that time only a few American universities taught this subject. Today more than a hundred American schools teach it and thousands of pupils learn its principles every year. It is not surprising, therefore, that, every four years or so, new editions of this work have been required. After three editions of it had been produced, Chandler re-wrote the fourth edition and gave it the title *An Introduction to Parasitology.* The book was again re-written in 1930, 1936 and 1940. Further rapid advances in our knowledge of parasitology have now made it necessary to re-write it yet again, although the arrangement of this seventh edition has not been extensively altered. Already in the sixth edition the scope of the book had been extended and an account of important parasites of domesticated animals had been included. This extension of the book's scope has been maintained and improved in this seventh edition, so that it now gives the reader a wide survey of parasitic animals, and is valuable to the veterinarian as well as to the biologist, although it still deals primarily with animals parasitic in man.

An outstanding feature of the book is its vigorous and stimulating style. The author evidently believes that a book of this kind should provide interesting reading as well as accurate information ; he has certainly succeeded in achieving this aim. At the same time he has remembered that his book is an introduction to parasitology rather than a text-book upon it. Emphasis has therefore been laid upon the biological aspects of the subject. We find, for example, that more space is devoted to life-histories, host-parasite relationships, epidemiological problems and to the principles of control and treatment which are based upon these, while relatively less is given to classification, morphology and nomenclature. Brief bibliographies at the end of each chapter introduce the reader to the vast literature on parasitology, so that he can readily study in more detail those aspects of it which interest him. At the end of the book there is a list of the leading journals in which papers upon various aspects of parasitology appear, and particular attention is called to the *Tropical Diseases Bulletin*, the *Veterinary Bulletin*, *The Review of Applied Entomology, Series B*, *The Journal of the American Medical Association*, *Biological Abstracts* and *Helminthological Abstracts*. " The six periodicals mentioned," says Chandler, " on account of their scope and thoroughness, are of inestimable value to anyone who attempts to keep pace with the progress of parasitology."

Every parasitologist will heartily endorse this tribute to these invaluable sources of information. Many of them will wish to add a tribute to the value of this book of Chandler's. It is a considerable achievement nowadays to follow in detail and to assess accurately the advances in our knowledge of even one group of Protozoa, Helminths or Arthropods. For this reason, perhaps, some books on parasitology omit either the Protozoa or the Arthropods which are associated with disease and concentrate upon only two of these three phyla, to which most of the animals parasitic in man and his domesticated stock belong. It is, therefore, especially useful to have in this book an adequate treatment of all these phyla. The biologist, too, who wishes to relate our knowledge of animals parasitic in man and his domesticated stock to his studies of those parasitic species which have no economic importance, will find in this book an admirable fusion of the biological and the economic points of view.

The book is well printed and handy to use. Some of the illustrations could be improved ; but most of them are adequate and no doubt it is the author's intention that they should be supplemented by observations made upon actual parasitic animals, which cannot be replaced by illustrations, however excellent these may be. There will be some readers, nevertheless, who cannot take laboratory courses in parasitology and the inclusion in future editions of some of the excellent photographs of parasitic animals which are now available would, no doubt, add to the value of the book. On the other hand, some teachers may prefer the line drawings with which this book is illustrated, because they cannot represent exactly the parasitic animal and therefore do not encourage the student to avoid making his own observations and drawings.

The book can be recommended to both the general public and to the biologist, who will be grateful to the author for guiding the earlier editions into this valuable fusion of readable text and accuracy of complicated information.

G. Lapage.

NEVEU-LEMAIRE, M. [Professeur agrégé des Facultés de Médecine]. **Traité de Protozoologie Médicale et Vétérinaire.** [Treatise on Medical and Veterinary Protozoology.] pp. xx + 844, 433 figs. 1943. Paris : Vigot Frères, Editeurs : 23 Rue de l'École-de-Médecine. [45s.]

Like its companion volumes on Helminthology and Entomology [this *Bulletin*, 1936, v. 33, 643 ; *ibid.*, 1938, v. 35, 931] this treatise on Protozoology

will undoubtedly be found to be a valuable and convenient book of reference. In fact the reviewer has already had occasion to consult it on several occasions and has obtained references which otherwise he would have had some difficulty in procuring. The book contains a vast amount of information on all aspects of medical and veterinary protozoology, much of it taken from obscure sources which are not frequently consulted ; but it is not up to date, even if allowance is made for the fact that the date of the author's preface is 1942. Very little reference is made, for instance, to the developments in knowledge regarding avian and simian malaria, and the many species of these parasites, including *P. knowlesi*, which have come to light in recent years are not mentioned. The importance of the exoerythrocytic cycle in malaria is passed over in a single line. One finds again the old statement that the sporozoite enters the red blood corpuscle. *P. ovale* is merely mentioned in a foot-note as being of doubtful validity, while little attention is given to the relationship of the three common human parasites to the similar forms in chimpanzees.

In general, the reviewer finds that the book covers very much the same ground as his own *Protozoology*, published in 1926, from which the author has borrowed many figures. The treatise under review, however, contains much that is not found in the reviewer's book. A considerable amount of space is devoted to consideration of symptomatology, pathology, treatment and prophylaxis of diseases due to protozoa. Over 120 pages are devoted to the intestinal ciliates of domestic animals and their relations—a proportion of the book which seems in excess of their importance. Nevertheless, for purposes of reference the account will prove of use. Again, under the heading *Treponema*—for, as is the custom, the spirochaetes and other non-protozoal organisms encountered in blood work are dealt with—90 species are mentioned, in most cases with reference only to the host. *Rickettsia* and rickettsial diseases receive 35 pages. Finally, as in the companion volumes, the book has a list of hosts and their parasites, a list of intermediate hosts and vectors and a list of vertebrate reservoirs, chiefly mammals. The book is well illustrated with 433 figures, and finishes with a fairly good index. *C. M. Wenyon.*

Dubois, A. **Chimiothérapie des trypanosomiases.** [Chemotherapy of Trypanosomiasis.] *Institut Royal Colonial Belge. Section des Sciences Naturelles et Médicales. Mémoires.* (Collection in-8°.) 1946, v. 15, No. 7, 169 pp. [258 refs.] [100 *fr.*]

The scope of this volume is severely limited. Apart from a few introductory sections on general aspects of the chemotherapy of trypanosomiasis, it deals in detail only with arsenicals and antimonials, excluding any consideration of mechanisms of drug action or general theory. A second publication is projected, to cover non-metallic preparations and general theoretical considerations.

In a prefatory note the author writes that the volume, prepared during the German occupation, served to support him during that painful period, but that the circumstances prevented him from keeping fully abreast of recent literature. Certain additions and alterations will therefore be necessary, but he has felt obliged to arrange for publication before making these changes, because of a journey to Africa. He intends, therefore, to produce a supplement, in due course, to set matters right. Those who will wish to use this book will certainly feel that they would have preferred to wait until it could be presented in a more finished form. A number of misprints are corrected in a page of errata at the end of the book, there is no table of contents, and, most serious of all, there is no index. An index is, of course, essential in a work of this nature, which is most likely to be used not as a book to be read from beginning to end, but as a volume to which one will resort, from time to time, in reference to a particular compound, chemotherapeutic problem, or author.

The introduction reminds the reader that practice, based on empiricism, has long preceded theoretical development, in the field of chemotherapy (as for example, in the time-honoured use of cinchona bark, mercury, etc.). The development of chemotherapy as an exact science was due in large part to researches on trypanosome infections. Whilst LINGARD and BRUCE, before the turn of the century, may be regarded as pioneers in the empirical chemotherapy of trypanosomiasis, and LAVERAN and MESNIL (1902) were the first to embark on systematic experimentation, EHRLICH, for his labours from 1903 to 1915, is undoubtedly to be hailed as the true founder of experimental chemotherapy. Apart from its outstanding theoretical value, his work with trypanosome infections was an essential stage towards the triumphal announcement of the first sound cure for syphilis.

The author writes that his compilation is intended to be of particular service to Belgian colonial medical officers, by placing at their disposal the facts known about preparations active against trypanosomiasis, both of man and of animals, and he then recalls, with justifiable pride, some of the unique contributions of Belgian workers towards the study of trypanosomiasis in the Congo. The Léopoldville laboratory, founded in 1899 under the inspiration of General DONNY, turned a major part of its attention to trypanosomiasis at its very inception, with VAN CAMPENHOUT as the first Director. His successor, BRODEN (1900–1911), together with RODHAIN, developed this interest still further. They conducted numerous field trials of compounds prepared by Ehrlich, and it was they who first introduced the practice of exhibiting tartar emetic intravenously in man. They were also pioneers (1908) in the evaluation of cerebrospinal fluid changes in sleeping sickness. MOUCHET and DUBOIS (1911–1912) were among the first to embark on itinerant mass-treatment, now one of the principal methods of sleeping sickness control. Miss PEARCE and VAN DEN BRANDEN conducted the first field trials of tryparsamide, and van den Branden, VAN HOOF and others have subsequently investigated numerous other products and therapeutic procedures. Human trypanosomiasis, which is the chief anxiety of the health service, remains at the present time in the forefront of the Léopoldville laboratory's activities.

The first section deals with general principles underlying the treatment of human trypanosomiasis, under the sub-headings of "Intercurrent diseases", "General rules of treatment", and "Follow-up after treatment". There follows a section entitled "Methods of experimental chemotherapy", dealing with experimental procedures in laboratory animals and *in vitro*, and including also a consideration of the normal course of infection in untreated human cases. A few pages follow to dismiss bismuth, gallium, indium, gold, rhodium and ruthenium, and the work then deals systematically first with arsenicals and then with antimonials.

The arrangement of material presented might perhaps be improved. For example, an explanation of the term "Chemotherapeutic index" follows immediately on the section headed "Experiments *in vitro*", instead of being included in the section for "Experiments *in vivo*". Again, having passed on from a general and detailed consideration of arsenicals to a similar treatment of the antimonials, one is then brought back to the arsenicals (with section-headings in printing-type which would suggest that we are still among the antimonials) for accounts of intrathecal treatment, intracarotid treatment, and ocular troubles after arsenical treatment.

Omissions and ambiguities are inevitable in a compilation of this nature, especially when prepared under such inauspicious circumstances. It would therefore be ungracious to pick on these, particularly when so much is reliably recorded. In any case, the wise reader will of course prefer, in his hour of need, to go to the original sources, liberally indicated by the author, who does not, however,

claim to give a complete bibliography, and admits to giving special notice to the publications of Belgian workers. His lists, together with those given in FINDLAY'S *Recent Advances in Chemotherapy* (London, Churchill, 1939) will guide the reader to all important literature-sources up to the outbreak of the recent war. The most exhaustive lists of references up to about 1934 are probably those in FISCHL and SCHLOSSBURGER'S *Handbuch der Chemotherapie* (Leipzig, Fischers, 1934).

Lest it be thought that this volume is received with unduly faint praise, let it be said that we will welcome the second volume, and will look forward to placing it on a near-by shelf, for easy access, together with this one—all the more so if it is to include an index to the entire work. *E. M. Lourie.*

FELSEN, Joseph [B.A., M.D., Director of Medical Research, Bronx Hospital, New York, etc.]. **Bacillary Dysentery, Colitis and Enteritis.** pp. xiv + 618, 145 figs. (2 coloured). 1945. Philadelphia & London: W. B. Saunders Company. [30*s.*]

This book is a review of our knowledge of all the aspects (clinical, pathological and epidemiological) of acute bacillary dysentery, chronic ulcerative colitis and distal ileitis. The author believes that chronic ulcerative colitis and distal ileitis are the late sequelae of acute bacillary dysentery and that their onset can often be traced to an attack of acute dysentery; he claims that from many such cases *Sh. flexneri* can be isolated. This opinion is based on experience in the U.S.A., where the incidence of Flexner dysentery and of chronic ulcerative colitis appear to be very much greater than in Britain.

The sections dealing with the symptomatology, diagnosis and treatment of these conditions are clear and up to date; the use of the sigmoidoscope and X-rays in diagnosis and in the control of treatment is advocated and there is a clear account of the sigmoidoscopic findings and radiological appearances in dysentery, colitis and other disorders of the bowel. There is, however, no mention of the precautions to be taken during the nursing of acute bacillary dysentery, either in hospital or at home, to prevent the spread of the disease to other persons.

The epidemiological and bacteriological aspects of bacillary dysentery are less satisfactorily described; the author uses the historical approach and frequently quotes the experiences of other workers with too little regard for differences in methods and material. In this way, parts of these sections have become merely a confused record of the conflicting findings of others. The description of the bacteriology of the *Shigella* group is no fuller than that given in the standard text-books and is made more confusing than is necessary by the use of an unfamiliar nomenclature, and by the importance given to biochemical rather than to serological reactions. The appendix that gives the technical methods for the isolation and identification of members of the *Shigella* group presupposes that the worker has available supplies of dehydrated media and commercial antisera. Other appendices deal with the control of dysentery in military establishments and in institutions.

The book contains a long and valuable bibliography in which over 2,000 references are quoted. *A. J. H. Tomlinson.*

NORMAN-WALKER, J. N. [C.I.E., M.R.C.S.(Eng.), M.R.C.P.(Lond.), D.T.M. & H. (Camb.)]. **Indian Village Health.** pp. iv+90, 8 plans & 2 diagrams. Indian Village Welfare Association. 1944. Humphrey Milford, Oxford University Press (Indian Branch). [4*s.*; *Rs.* 2-8.]

This unpretentious, but attractive, little book has been written partly as a guide to doctors engaged on public health work, but chiefly with the object

of enlisting the intelligent co-operation of local authorities, voluntary organizations, and the people themselves, in improving health conditions in Indian villages. The author has exceptional qualifications for producing such a book. After a distinguished career in the regular lines of activity of an officer of the Indian Medical Service, he was selected for the important work of reorganizing the medical and health departments of the great State, Hyderabad, in South India, and for a number of years he carried out this task with conspicuous success. He writes, therefore, in the light of practical experience of the problem, and deals, not with what might be accomplished with the help of ample funds, a highly skilled staff and an enlightened public, but with what can be done in the absence of these advantages. He has confined his attention to the diseases " amenable to general measures in which the assistance of civil authorities and village workers can be really useful," and has strictly avoided the use of technical language.

The causes and methods of control of the chief infectious diseases are dealt with in 45 pages ; there is a brief chapter on personal protection against disease, one on the organization of public-health activities, and another on building regulations and the construction of minor public works. In an appendix instructions are given for the control of plague. A special feature of the book is the reproduction of detailed plans of a tuberculosis clinic, an infant-welfare centre, a slaughter house, a vegetable market, a meat market, a beef shop, a village well, and an " aqua privy ". These plans are reproduced on a very small scale, but they will be found very helpful to officers of health and engineers who have to undertake the construction of such works without previous experience.

The present volume is a reprint of the first edition, which was published in 1943, and probably written in 1942, so that some important recent advances, such as the use of DDT, are not mentioned.

Although certain details of the methods recommended are open to criticism by experts, the book can be read with profit by everyone who is concerned with the health of villages in India and other tropical countries. It is to be hoped that other public-health workers in the tropics will be stimulated to produce books, dealing, on similar lines, with the special conditions of the areas in which they work. *John W. D. Megaw.*

COUPLAND, Reginald [K.C.M.G., C.I.E., Hon.D.Litt. (Durham), etc.]. **Livingstone's Last Journey.** 271 pp., 5 maps & 2 pls. 1945. London : Collins, 14 St. James's Place. [12*s.* 6*d.*]

Although this book is not primarily of medical interest, readers of this *Bulletin* who have followed the literature on Livingstone, or who desire a succinct account of this period of his life, will be glad to know of the existence of this most readable book. There is evidence of a vast amount of research, but the writing is so clear that scholarship does not obtrude itself, and the story holds the attention of the reader throughout. *Charles Wilcocks.*

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